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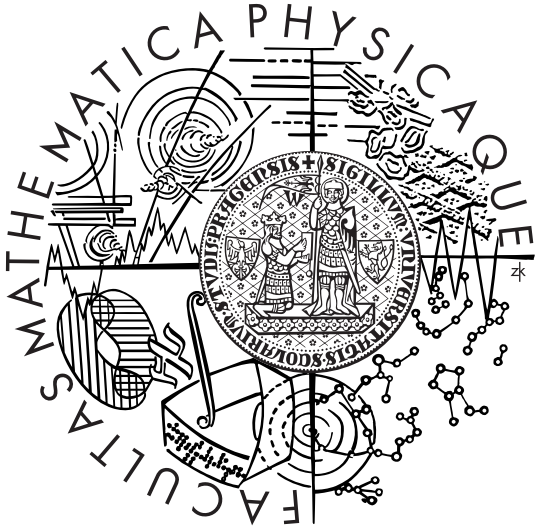

Pavol Krasnovský

DETERMINISTICKÉ A STOCHASTICKÉ MODELY V MOLEKULÁRNÍ A BUNĚČNÉ BIOLOGII

Katedra pravděpodobnosti a matematické statistiky

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Studijní program:	Matematika
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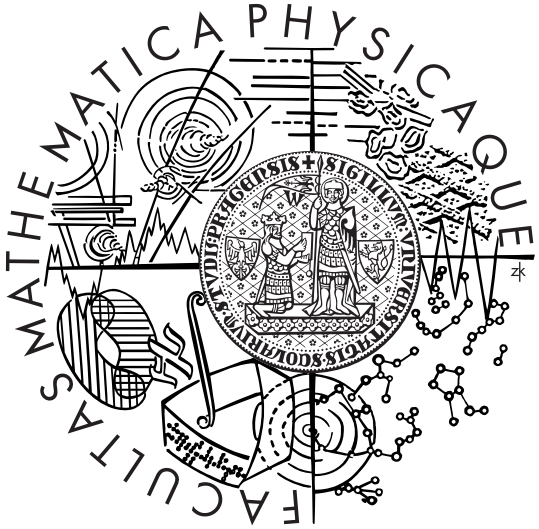

Pavol Krasnovský

DETERMINISTIC AND STOCHASTIC MODELS IN MOLECULAR AND CELL BIOLOGY

Department of Probability and Mathematical Statistics

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Největší dík patří mé rodině za duchovní a morální podporu během studií.

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Abstrakt: V předložené práci se zabýváme hlavními metodami, které se používají při modelování vývoje počtu molekul v buňce. Tyto modely bývají především využívány pro výpočet dvou základních charekteristik chemického systému, kterými jsou přechodová pravděpodobnostní funkce a hustota invariantní míry. Abychom tyto dvě charakteristiky mohli spočítat, je nutné vzít v úvahu několik podmínek, které daný chemický systém musí splňovat. Proto je součástí této práce i stručný přehled ergodické teorie a teorie invariantní míry. Tyto teorie jsou následně použité ve dvou ilustrativních příkladech, v nichž ověřujeme nutné a postačující podmínky pro výpočet výše zmíněné přechodové pravděpodobnostní funkce a hustoty invariantní míry pro dva druhy chemického systému. Přechodovou pravděpodobnostní funkci a hustotu inveriantní míry pak získáme numerickým řešením Fokker-Planckovi rovnice, která je jak v dynamické tak i stacionarní podobě. Následně jsme schopni získané výsledky porovnat s výsledky Monte Carlo simulace a jak je z přiložených obrázků zřejmé, daná řešení jsou v podstatě identická. V závěru práce dále formulujeme a následně analyzujeme chemický systém, který představuje napadnutí lidské buňky virem chřipky. Vzhledem k tomu, že tento systém je podstatně složitější, využíváme pro výpočet Monte Carlo metodu. Avšak zároveň tento problém definujeme i pomocí stochastické diferencialní rovnice s náhodnými koeficienty, a takto definovaný problém je možné použít pro další výzkum.
Klíčová slova: Hustota invariantní míry, Fokker-Planckova rovnice, ergodické řešení, chemické reakční funkce, Monte Carlo simulace.

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Abstract: This thesis presents the main methods that are used to model the time evolution of the number of molecules in a cell. Two of the main aims in cell biology are to compute first the transition probability function and second the density of the invariant measure. These two problems imply a number of conditions and hence we also include the ergodic theory and theory of the invariant measure. We use two illustrative examples of the application of the previously mentioned theories. We verify the necessary and sufficient conditions for the computation of the transition probability function and the density of the invariant measure in case of two types of a chemical system. The probability function and the density are then given by a numerical solution to the Fokker-Planck equation in both the dynamic and the stationary case. Furthermore, we compare the obtained solutions to the results from the

Monte Carlo simulation. We find that the solutions give almost identical results as the Monte Carlo simulation. At the end of this thesis, we formulate and analyze a chemical system represented by a human cell infected by an influenza virus. Given the complexity of the system, we compute the results using the Monte Carlo method. In addition we define this problem by a stochastic differential equation with random coefficients. This formulation can be used for further research.

Keywords: The density of invariant measure, the Fokker-Planck equation, the ergodic solution, chemical rate function, the Monte Carlo method.

Chapter 1

Introduction

There has recently been a number of pioneering studies of biochemical processes in cells combining experiments with quantitative modeling to explain genetic regulation, cell cycle or circadian rhythms. The pioneering approaches were proposed by [Gillespie (1977)], [Haseltine et al. (2002)], [Gillespie (2006)] or [Kevrekidis et al. (2003)]. All these studies introduce new quantitative methods which allow us to create better and more precise models of chemical processes in cells.

There are two main approaches to modeling biochemical process in cells. Those are the fine-grained and the coarse-grained descriptions of a system. Choosing between them involves a number of trade-offs. "On the one hand, constructing a coarser-grained model will often rely on extensive prior intuition about the cellular phenomenon. On the other hand, a finer-grained model could require more detailed prior information about the properties of the individual components" [Mogliner et al. (2006)]. With respect to the fine-grained approach, the most used models are the Gillespie Stochastic Simulation [Gillespie (1977)], the Gibson-Bruck Stochastic Simulation [Gibson (2000)] and the Optimized Direct Method [Cao (2004)]. Another approach, which does not cumulate errors in simulations, uses parallel computing, for instance Graphics Processing Units [Klingbeil (2010)]. On the other hand, the coarse-grained models are mostly based on the system of ordinary differential equations and stochastic differential equations. The latter serve as a bridge between the discrete stochastic simulations and the deterministic reaction rate equations.

Why is the quantitative approach in cell biology so needed? A cell is a sophisticated living organisms and contains many kinds of molecules. When a cell is sufficiently saturated by molecules, the molecules start to interact with each other. These interactions are called chemical reactions. The aim of a quantitative description of biological systems is to enable us to obtain models that are more reliable and precise and that deepen our understanding of the real processes in the cell. Thus, we can adequately describe observed noise, variability and heterogeneity of the systems. Furthermore, we can use stochastic methods in order to check quantitatively for the proposed molecular mechanisms. These methods can raise new questions and thus they inspire new experiments, leading us down the ways we have not thought we could explore. There are many interesting and sophisticated events in a cell that we can analyse in this thesis, we will use mathematical tools to describe a few interesting problems. One of this problem namely influenza evolution has not been tackled yet, we hope that our work will be a useful contribution to the current literature. Hereafter, we offer a more detailed overview of the organization of the thesis.

In Chapter 2, we shortly introduce main approaches which are used for modeling chemical processes in cell biology, in particular the deterministic method, Monte Carlo simulation, master equation, Langevin equation and Fokker-Plank partial differential equation. We also describe the numerical solutions to the previously mentioned methods. Furthermore, we formulate two types of chemical systems for which we find the numerical solution. The first one is a one dimensional switch and the second one a synthesis of two metabolites. As an illustration of the previously mentioned modeling approaches, we program these methods in the MATLAB language and then apply them to the two types of the chemical systems that we suggested. At the end of this chapter, we compare the results that we obtained.

Since one of the main aims of quantitative modeling in cell biology is to find stationary distributions of chemical systems, Chapter 3 is concerned with the conditions that need to be satisfied in order to find them. We first need to present the theory of the existence of the invariant measure of the solution. A necessary condition for the existence of the invariant measure is regularity and thus we also include the theory of the regularity of the solution. For reader's comfort, we also provide the proofs of these theorems that are key to our analysis. Since we compute the transition probability function as the solution to the Fokker-Planck equation in dynamic case, we also rigorously verify that this construction is correct. Consequently, we verify that all the conditions for the existence of the invariant measure hold in our two chemical systems that we defined in the previous chapter. We compute the densities of invariant measure for both chemical systems as the solution to the Fokker-Planck equation in stationary case. We compare these solutions with the Monte Carlo simulations.

After reviewing the theoretical background of our analysis, we deal with the modeling of the chemical reactions themselves in Chapter 4. We use an illustrative example of a chemical system, in particular we depict the infection of a human body by an influenza virus. At the beginning of this chapter, we describe the behavior of a reduced chemical system that represents the chemical reactions of human body in cell before and after it is infected by the influenza virus. First, given the nature of the problem, we specify reaction rates as functions depending on a time variable. Second, the time when the influenza virus defeats the immunity system of the human body is a random variable. Consequently, the Langevin Itô differential equation now depends not only on a space variable but also on the random time variable. We obtained the results using Monte Carlo simulation. Since, to our knowledge, such kind of a chemical system has not been solved yet, we also formulate the Langevin equation of this chemical system for following research.

There are several studies that served as an inspiration to our analysis. The most helpful papers concerned with the deterministic and stochastic modeling in cell biology, and the numerical solution of partial differential equations are mostly collected from [Erban et al. (2009) [Kampen (1992)] and [Hoffman (2001)]. Materials for the regularity of solution and the existence of the invariant measure of the solution are taken from [Khasminskii (2011)], [Strook (2005)], [Soize (1994)] and [Seidler (2011)]. To define the influenza problem, [Jefferson, et al. (2012)], [Solomon (2001)] and [Anthony (1998)] were the most insightful and constructive for our purpose.

Chapter 2

Deterministic and Stochastic Models of the Cell Behavior

The time evolution of a concentration of molecules is often described by ordinary differential equations. This is mostly possible because we assume a homogeneous spatial distribution of the molecules, relying on a fast diffusion within a given cell. Such an approach is justified by tests with billions of molecules, usually carried out in an artificial environment. However, there are many problems in cell biology that only concern small numbers of molecules. The above mentioned method is thus not suitable since the spatial distribution cannot be assumed to be homogeneous ad hoc. Hence, a modeler needs to explicitly take into account the stochastic nature of such processes in a cell.

There are several alternatives for the computation of the probability distribution of the number of molecules in a cell. One of them is the chemical master equation (2.7) which describes the exact behavior of the chemical system. This equation has N dimensions if there are N molecular species in whose probability distribution within a cell we may be interested. Those equations are often computed only for $N = 3$ or $N = 4$ at most because large dimensions require a lot of memory and computational work. Thus, even a low number of molecular species would involve such a demanding computational power that the practicality of this becomes questionable.

A suitable method for the case of more dimensions is the Monte Carlo method. This approach is appropriate especially when one is interested in the steady state solution of the probability distribution. A good approximation of the probability distribution emerges when the reactions in the cell are simulated using random numbers. Then, the number of molecules of each of the species $\boldsymbol{x}$ is sampled as the time progresses. This approximation was discovered by Gillespie [Gillespie (1977)] and it is called the Gillespie's algorithm. Since our problem does not exceed two dimensions, we do not need to use the Monte Carlo simulation, nor the algorithm for its approximation. Nonetheless, these methods can be used to investigate whether they provide similar results as the master equation approach. This insight is certainly valuable as it can serve as a kind of control of our computations.

Finally, the above mentioned chemical master equation can be approximated by the Fokker-Plank equation (2.11). Furthermore, its approximate solution can be computed by the finite difference method which reduces the work substantially since we need fewer grid points in each dimension. However, the dimension of this partial differential equation still corresponds to the number of involved chemical species. When this number is high, the finite difference

method is not efficient and the Monte Carlo approach is the only feasible possibility. The solution to the Fokker-Plank equation, a linear, scalar and time-dependent differential equation, is the probability density of the number of molecules in a given cell. Thus it is directly comparable to the results obtained using the previously described methods.
The following chapter will present the chemical reaction model together with the reaction rate equations, the master equation, the Langevin equation and the Fokker-Planck equation. These equations will be written explicitly for a one dimensional switch system (2.1) and a chemical system with two reacting components (2.4). The results of the Gillespie's algorithm and the numerical solution to the Fokker-Plank equation are compared and evaluated at the end of this section.
The literature that we drew most inspiration from in: [Kampen (1992)], [Hoffman (2001)] and [Sjöoberg, et al. (2009)].

2.1 Equations for Chemical Reaction Models

This section will present the stochastic and deterministic descriptions of chemical reactions in a cell. We claimed in the introductory section that the concentrations of the molecules, when viewed on a macroscale, can be described by a system of ordinary differential equations. However, when we look at the system from the mesoscale perspective, we need to use the chemical master equation for the probability distribution of the numbers of the participating molecules. The approximation of the solution to the master equation is the solution to its approximated scalar partial differential equation, the Fokker-Plank equation.

2.1.1 Deterministic Equations

First, suppose we take the macroscopic description of the chemical reaction model with M chemically active molecular species. This specification requires us to assume that the reactor is well mixed so that the molecules' mixture is spatially homogeneous. Thus we do not need to take into account the possible dependence of the distribution on space. This system with a large number of molecules of each species is far from chemical instability and the time evolution of the average concentrations of the molecules can be described by a system of M coupled nonlinear ordinary differential equations [Elf et al. (2003)]. In addition, we will use the average numbers of molecules instead of average concentrations since this is more computationally convenient. We also assume a constant volume of the reactor.
Let us introduce the following two examples.

One-dimensional chemical switch model
We assume a one-dimensional chemical switch model. Let the concentration of the only involved chemical species X at time t be denoted x. Then the one-dimensional chemical switch model consists of the following chemical reactions:

$$\emptyset \xrightarrow{\lambda_1} X \xrightarrow{\mu_1} \emptyset \qquad 2X \xrightarrow{\lambda_2} 3X \xrightarrow{\mu_2} 2X. \tag{2.1}$$

The species are produced with the intensities λ_1 and λ_2. They are annihilated with the intensities μ_1 and μ_2. When we use the term "produce" we mean that the number of chemical species X grows. On the other hand, "annihilation" means that the number of molecules

decreases. The classical deterministic description of the chemical system (2.1) is given by the following mean-field ordinary differential equation:

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda_1 - \mu_1 x(t) + \lambda_2 x^2(t) - \mu_2 x^3(t). \tag{2.2}$$

The coefficients in the system are chosen in such a way that the solution of equation (2.2) has two steady state:

$$\lambda_1 = 2250, \qquad \lambda_2 = 0.18, \qquad \mu_1 = 37.5, \qquad \mu_2 = 2.5 \times 10^{-4}. \tag{2.3}$$

The synthesis of two metabolites
We suppose the synthesis of two metabolites X and Y, which are subjected to the following set of chemical reactions:

$$X + X \xrightarrow{\mu} \emptyset \qquad X + Y \xrightarrow{\theta} \emptyset \qquad \emptyset \xrightarrow{\lambda_1} X \qquad \emptyset \xrightarrow{\lambda_2} Y. \tag{2.4}$$

The chemical species are created by intensity λ_1 and λ_2, annihilated with the intensities μ and they react with each other with intensity θ.

The corresponding deterministic description of the chemical system (2.4) is given by the system of ordinary differential equations:

$$\begin{aligned} \frac{\mathrm{d}x(t)}{\mathrm{d}t} &= -\mu x(t)(x(t)-1) - \theta x(t) y(t) + \lambda_1, \\ \frac{\mathrm{d}y(t)}{\mathrm{d}t} &= -\theta x(t) y(t) + \lambda_2. \end{aligned} \tag{2.5}$$

We chose the values of coefficients as

$$\mu = 10^{-3}, \qquad \theta = 10^{-2}, \qquad \lambda_1 = 1.2, \qquad \lambda_2 = 1. \tag{2.6}$$

2.1.2 The Master Equation

The master equation is an equation for the probability distribution $p(t, \boldsymbol{x})$ that a certain number $\boldsymbol{x}$ of molecules of each species is present at time t [Kampen (1992)].

Let a state $\boldsymbol{x} \in \mathbb{S}^N$ where $N \geq 0$ is the number of molecular species or the dimension of the problem and $\mathbb{S} = \mathbb{Z}^+$, the non-negative integer numbers. An elementary chemical reaction is a transition from state $\boldsymbol{x}_2$ to state $\boldsymbol{x}_1$. Chemical species interact through $M \geq 1$ chemical reactions R_j, $j = 1, \ldots, M$. Each reaction R_j can be described by a step $\boldsymbol{\nu}_j$ in $\mathbb{S}^N$. The probability per unit time for transition from $\boldsymbol{x}_2$ to $\boldsymbol{x}_1$, caused by reaction R_j, or the reaction propensity, is $\alpha_j(\boldsymbol{x}_2)$ and $\alpha : \mathbb{S}^N \to \mathbb{R}$. One reaction R_j can be written as

$$\boldsymbol{x}_2 \xrightarrow{\alpha_j(\boldsymbol{x}_2)} \boldsymbol{x}_1, \qquad \boldsymbol{\nu}_j = \boldsymbol{x}_2 - \boldsymbol{x}_1.$$

The master equation for $p(t, \boldsymbol{x},)$ with M reactions can be written in the following manner

$$\frac{\partial}{\partial t} p(t, \boldsymbol{x}) = \sum_{j=1}^{M} \Big[\alpha_j(\boldsymbol{x} + \boldsymbol{\nu}_j) p(t, \boldsymbol{x} + \boldsymbol{\nu}_j) - \alpha_j(\boldsymbol{x}) p(t, \boldsymbol{x}) \Big]. \tag{2.7}$$

The computational difficulty with this equation is that it is in fact an infinite system of ordinary differential equations. Let us now consider system (2.1). Let x denotes the number

of X molecules. We denote $X(0) = x$. Then the master equation of chemical system 2.1 can be written as:

$$\begin{aligned}\frac{\partial p(t,x)}{\partial t} &= \lambda_1 p_{x-1}(t,x) - \lambda_1 p_x(t,x) + \mu_1 p_{x+1}(t,x) - \mu p_x(t,x) \\ &+ \lambda_2(x-1)(x-2)p_{x-1}(t,x) - \lambda_2 x(x-1)p_r(t,x) + \mu_2(x+1)x(x-1)p_{x+1}(t,x) \\ &- \mu_2 x(x-1)(x-2)p_x(t,x).\end{aligned} \tag{2.8}$$

Let us now consider system (2.4). Let x and y denote the number of molecules X and Y. Master equation for chemical system 2.4 for initial conditions $X(0) = x_1$ and $Y(0) = x_2$ can be written as:

$$\begin{aligned}\frac{\partial p(t,x,y)}{\partial t} &= \mu_1(x+2)(x+1)p(t,x,y)_{x+2,y} - \mu_1 x(x-1)p(t,x,y) \\ &+ \mu_2(x+1)(y+1)p_{x+1,y+1}(t,x,y) - \mu_2 xy p_{x,y}(t,x,y) \\ &+ \lambda_1 p_{x-1,y}(t,x,y) - \lambda_1 p_{x,y-1}(t,x,y) - \lambda_2 p_{x,y}(t,x,y).\end{aligned} \tag{2.9}$$

Here we use a convention that $p_{r,s}(t,x,y) = 0$ if $r < 0$ or $s < 0$.

2.1.3 The Langevin Equation

Considering the integer valued vector $\boldsymbol{x}$ as a real variable, Gillespie [Gillespie (2006)] derived the chemical Langevin equation by approximating Poisson random variables by normal random variables. This approximation is possible if many reaction events happen before the propensity functions significantly change their values; see [Gillespie (2006)] for details. Let $(\Omega, \mathcal{F}, (\mathcal{F}_t), \mathrm{P})$ be a stochastic basis with filtration which complies usual conditions (3.1). The chemical Langevin Itô equation can be written in the form

$$\mathrm{d}X_i = \left(\sum_{j=1}^{M} \nu_{ji}\alpha_j(\boldsymbol{X}(t))\right)\mathrm{d}t + \sum_{j=1}^{M} \nu_{ji}\sqrt{\alpha_j(\boldsymbol{X}(t))}\mathrm{d}W_j, \qquad j = 1, 2, \ldots, M. \tag{2.10}$$

where W_j, $j = 1, 2, \ldots, M$ are one-dimensional $(\mathcal{F}_t)$- Wiener processes and ν_{ji} is the change in the number of X_i produced by one reaction R_n. Notice that this equation is in the form (3.1).

2.1.4 The Fokker-Planck Equation

The Fokker-Planck equations can be derived in two ways. First, we derived it from master equation (2.7). By truncating the Taylor expansion of the master equation (2.7) after the second order term we arrive at the Fokker-Planck equation [Kampen (1992)]. Let $\mathcal{H}(f)$ denote the Hessian matrix of second derivatives of f with respect to $\boldsymbol{x} \in \mathbb{R}_+^N$. Then the equation is

$$\begin{aligned}\frac{\partial p(t,\boldsymbol{x})}{\partial t} &= \sum_{j=1}^{M} \boldsymbol{\nu}_j \cdot \nabla_x(\alpha_j(\boldsymbol{x})p(t,\boldsymbol{x})) + \frac{1}{2}\boldsymbol{\nu}_j \cdot \mathcal{H}(\alpha_j(\boldsymbol{x})p(t,\boldsymbol{x}))\boldsymbol{\nu}_j \\ &= \sum_{i=1}^{N} \frac{\partial}{\partial x_i}\Big[-\Big(\sum_{j=1}^{M} \nu_{ji}\alpha_j(\boldsymbol{x})\Big)p(t,\mathbf{x})\Big] + \frac{1}{2}\frac{\partial^2}{\partial x_i^2}\Big[\Big(\sum_{j=1}^{M} \nu_{ji}^2\alpha_j(\boldsymbol{x})\Big)p(t,\mathbf{x})\Big] \\ &+ \sum_{k<i} \frac{\partial^2}{\partial x_i \partial x_k}\Big[\Big(\sum_{j=1}^{M} \nu_{ji}\nu_{jk}\alpha_j(\boldsymbol{x})\Big)p(t,\mathbf{x})\Big].\end{aligned} \tag{2.11}$$

Second method of derivation of the Fokker Planck equation can be achieve through Feyman-Kac formula. For detail information see [Øksendal (2007)]. The Fokker-Planck equation of the chemical system (2.1) is after Taylor expansion of (2.7)

$$\frac{\partial p(t,x)}{\partial t} = \frac{\partial^2}{\partial x^2}\Big(\sigma(x)p(t,x)\Big) - \frac{\partial}{\partial x}\Big(b(x)p(t,x)\Big), \tag{2.12}$$

where the drift and diffusion coefficients are

$$\begin{aligned} b(x) &= \lambda_1 - \mu_1 x + \lambda_2 x(x-1) - \mu_2 x(x-1)(x-2) \\ \sigma(x) &= \frac{\lambda_1 + \mu_1 x + \lambda_2 x(x-1) + \mu_2 x(x-1)(x-2)}{2}. \end{aligned} \tag{2.13}$$

The Fokker-Planck equation of the chemical system (2.4) is

$$\begin{aligned} \frac{\partial p(t,x,y)}{\partial t} &= \frac{\partial^2}{\partial x^2}\Big(\sigma_x(x,y)p(t,x,y)\Big) + \frac{\partial^2}{\partial y^2}\Big(\sigma_y(x,y)p(t,x,y)\Big) + \frac{\partial^2}{\partial x \partial y}\Big(\sigma_{xy}(x,y)p(t,x,y)\Big) \\ &\quad - \frac{\partial}{\partial x}\Big(b_x(x,y)p(t,x,y)\Big) - \frac{\partial}{\partial y}\Big(b_y(x,y)p(t,x,y)\Big), \end{aligned} \tag{2.14}$$

where the drift coefficients are following

$$b_x(x,y) = -\mu_1 x(x-1) - \mu_2 xy + \lambda \qquad b_y(x,y) = -\mu_2 xy + \lambda_2, \tag{2.15}$$

and diffusion coefficients are

$$\sigma_x(x,y) = \frac{\mu_1 x(x-1) + \mu_2 xy + \lambda_1}{2} \qquad \sigma_y(x,y) = \frac{\mu_2 xy + \lambda_2}{2} \qquad \sigma_{xy}(x,y) = \mu_2 xy. \tag{2.16}$$

The boundary conditions at the lower boundaries are by assumption $p(t,\mathbf{x}) = 0$ for $\boldsymbol{x}_j = 0$, $j = 1,\ldots,M$. It is shown in [Kampen (1992)] that for large systems with many molecules the solution can be expanded in a small parameter where the zero-order term is the solution to the deterministic reaction rate equations and the first perturbation term is the solution of a Fokker-Planck equation.

2.2 Methods for Numerical Solution

In this section, we describe the numerical solution to the particular methods which we use to solve the equations that we defined in the previous section.

2.2.1 Solving the Ordinary Differential Equations

The numerical solution to the system of the ordinary differential equations is a well-known and strait forward process. In this thesis, we apply function ODE23s from the MATLAB program to solve the system of the ordinary differential equations (2.2), (2.5), (4.5) and (4.6). In Chapter 4, we solve system of ordinary differential equations (4.6) with a parameter depending on time. Therefore, we program an auxiliary object class. We can recommend the book [Butcher (2008)] for more detailed information.

2.2.2 Gillespie's Method

A Monte Carlo method for stochastic simulation of trajectories in time of the behavior of chemical reactions was invented by Gillespie [Gillespie (1977)]. We apply the Gillespie Stochastic Simulation Algorithm to the following chain of general chemical reactions:

$$X_1 \xrightarrow{\mu_1} X_2 \xrightarrow{\mu_2} X_3 \xrightarrow{\mu_3} \dots \xrightarrow{\mu_{N-1}} X_N \qquad X_1 \xleftarrow{\mu_N} X_2 \xleftarrow{\mu_{N+1}} X_3 \xleftarrow{\mu_{N+2}} \dots \xleftarrow{\mu_{2N-2}} X_N \tag{2.17}$$

The algorithm for advancing the system in time is:

1. Generate two random numbers r_1, r_2 uniformly distributed in $(0, 1)$.
2. Compute propensity functions $\alpha_n = X_n \mu_n$ for $n = 1, 2, ..., N-1, N, N+1, \dots, 2N-2$ and
$$\alpha_0 = \sum_{n=1}^{2N-1} \alpha_n.$$
3. Compute the time at which the next chemical reaction takes place as $t + \tau$ where $\tau = \frac{1}{\alpha_0} \ln\left[\frac{1}{r_1}\right]$.
4. If $r_2 < \sum_{n=1}^{2N-1} \frac{\alpha_n}{\alpha_0}$, then for $n \neq j$ and $n \neq j+1$ such that
$$r_2 \geq \frac{1}{\alpha_0} \sum_{n=1}^{j-1} \alpha_n \qquad \text{and} \qquad r_2 < \frac{1}{\alpha_0} \sum_{n=1}^{j} \alpha_n.$$
Then compute the number of molecules at time $t + \tau$ by
$$\begin{aligned} X_j(t+\tau) &= X_j(t) - 1, \\ X_{j+1}(t+\tau) &= X_{j+1}(t) + 1, \\ X_n(t+\tau) &= X_n(t), \quad \text{for} \quad j \in \{1, \dots, N-1\}. \end{aligned}$$
5. Then compute the number of molecules at time $t + \tau$. If $j \leq N - 1$ then
$$\begin{aligned} X_j(t+\tau) &= X_j(t) - 1, \\ X_{j+1}(t+\tau) &= X_{j+1}(t) + 1, \\ X_n(t+\tau) &= X_n(t), \quad \text{for} \quad j \in \{1, \dots, N-1\}. \end{aligned}$$
If $j \geq N$ then
$$\begin{aligned} X_{j-N+1}(t+\tau) &= X_{j-N+1}(t) + 1 \\ X_{j-N+2}(t+\tau) &= X_{j-N+2}(t) - 1 \\ X_n(t+\tau) &= X_n(t) \quad \text{for} \quad n \neq j - N = 1 \quad \text{and} \quad n \neq j - N + 2. \end{aligned}$$
6. Continue with step (5) for time $t + \tau$.

The time step τ computed in step 3. is the waiting time for next chemical reaction. For stiff problems, the expected value of τ is small and the progress is slow, similar to what it is for an explicit, deterministic ordinary differential equation integrator. One way of circumventing these problems is found in [Rathinam et al. (2003)].

2.2.3 Solving the Fokker-Planck Equation

The numerical solution to the nonlinear Fokker-Planck equation has been a challenging problem for a long time. Various approaches have been introduced to tackle this problem. In this thesis, we subsequently solve a one-dimensional Fokker-Planck equation (2.12) and a two-dimensional Fokker-Planck equation (2.14). The equations are both solved the same way as one would solve a stationary equation (2.19) and a time evolution equation 2.14. In this part, we provide a short explanation of the numerical solution to one-dimensional stationary equation (2.19) for chemical system (2.1) and also the numerical solution to the Fokker-Planck equation (2.14) for chemical system (2.4).

Numerical Solution to the Stationary Equation of Chemical System (2.1)

The stationary distribution $P_s(x) = \lim_{t\to\infty} p(t,x)$ is a solution to the stationary equation namely

$$\begin{cases} 0 = \dfrac{\mathrm{d}^2}{\mathrm{d}x^2}\Big(\sigma(x)P_s(x)\Big) - \dfrac{\mathrm{d}}{\mathrm{d}x}\Big(b(x)P_s(x)\Big) \\ P_s(x) \to 0 \quad \text{as} \quad x \to \infty \end{cases} \tag{2.18}$$

where $b(x)$ and $\sigma(x)$ are drift and diffusion coefficients (2.13). Integrating over x, we get

$$P_s(x) = \frac{c}{\sigma(x)} \exp\left[\int_0^x \frac{b(y)}{\sigma(y)}\mathrm{d}y\right], \tag{2.19}$$

where c is the constant, which we get by the normalization $\int_{\mathbb{R}} P_s(x)\mathrm{d}x = 1$. To numerically evaluate integral in equation (2.19) with coefficients (2.13), we use numerical function QUAD in the MATLAB program.

Numerical Solution to the Dynamic Equation of Chemical System (2.4)

Suppose two dimensional non-stationary differential equation defined in the following manner

$$\begin{cases} \dfrac{\partial p}{\partial t} = \dfrac{\partial^2}{\partial x^2}(\sigma_x p) + \dfrac{\partial^2}{\partial y^2}(\sigma_y p) + \dfrac{\partial^2}{\partial x \partial y}(\sigma_{xy}(p)) - \dfrac{\partial}{\partial x}(b_x p) - \dfrac{\partial}{\partial y}(b_y p) \\ p(x,y,0) = p_0(x,y) \qquad (x,y) \in Z \\ \displaystyle\int_0^\infty \int_0^\infty P_s(x,y)\mathrm{d}x\mathrm{d}y = 1, \end{cases} \tag{2.20}$$

in domain $Z \times [0,T] = [0,X] \times [0,Y] \times [0,T]$, with boundary condition

$$p = 0 \qquad \text{in} \qquad \partial Z \times [0,T]$$

where $X, Y, T > 0$, $p(t,x,y) = p$ and coefficients $b_x(x,y)$, $b_y(x,y)$, $\sigma_x(x,y)$, $\sigma_y(x,y)$, $\sigma_{xy}(x,y)$ are of the form (2.15) and (2.16) respectively. As the initial distribution we choose bivariate normal distribution $N(\boldsymbol{\mu}, \boldsymbol{\Sigma})$. We solve this partial differential equation (2.20) by the finite difference method. We use algebraic finite difference approximations of the derivatives involved in equation (2.20) and we develop an explicit finite difference scheme that provides us with an approximate solution to this partial differential equation (2.20). First, we discretize the continuous domain where the partial differential equation (2.20) is considered, into a discrete difference grid. Therefore, we choose spatial step $h > 0$ and time step $\tau > 0$. Then the

spatial grid is of the form $0 = x_1 < x_2 < \cdots < x_I = X$, $0 = y_1 < y_2 < \cdots < y_J = Y$, where $h = x_{i+1} - x_i = y_{j+1} - y_j$, for $i = 1, \ldots, I-1$ and for $j = 1, \ldots, J-1$. The time interval $[0, T]$ is also discretized in the following way $0 = t_1 < \cdots < t_N = T$, where $\tau = t_{k+1} - t_k$ for $k = 0, \ldots, K-1$. Now, we use finite difference approximations to approximate derivatives in (2.20). We denote $p(x_i, y_j, t_k) \approx P^k_{i,j}$, then we get the following formulas

$$\begin{aligned}
\frac{\partial p}{\partial t}(x_i, y_j, t_n) &\approx \frac{P^{n+1}_{i,j} - P^n_{i,j}}{t}, \\
\frac{\partial p}{\partial x}(x_i, y_j, t_n) &\approx \frac{P^{n+1}_{i+1,j} - P^n_{i-1,j}}{2h}, \\
\frac{\partial p}{\partial y}(x_i, y_j, t_n) &\approx \frac{P^{n+1}_{i,j+1} - P^n_{i,j-1}}{2h}, \\
\frac{\partial p}{\partial x^2}(x_i, y_j, t_n) &\approx \frac{P^n_{i+1,j} + 2P^n_{i,j} - P^n_{i-1,j}}{h^2}, \\
\frac{\partial p}{\partial y^2}(x_i, y_j, t_n) &\approx \frac{P^n_{i,j+1} + 2P^n_{i,j} - P^n_{i,j-1}}{h^2}, \\
\frac{\partial p}{\partial xy}(x_i, y_j, t_n) &\approx \frac{P^n_{i+1,j+1} - P^n_{i-1,j+1} - P^n_{i+1,j-1} + P^n_{i-1,j-1}}{4h^2},
\end{aligned} \tag{2.21}$$

where $i = 2, \ldots, I-1$, $j = 2, \ldots, J-1$ and $\mu = \frac{\tau}{h^2}$. We solve this finite difference scheme subsequently for $n = 2, \ldots, N-1$. We get the initial state P^0 from the initial condition function p_0. We also use the finite difference method in modified form to solve the stationary partial differential equation for chemical system (2.4) in the following manner

$$\begin{cases} 0 = \dfrac{\partial^2}{\partial x^2}(\sigma_x p) + \dfrac{\partial^2}{\partial y^2}(\sigma_y p) + \dfrac{\partial^2}{\partial x \partial y}(\sigma_{xy} p) - \dfrac{\partial}{\partial x}(b_x p) - \dfrac{\partial}{\partial y}(b_y p) \\ \displaystyle\int_0^\infty \int_0^\infty P_s(x, y) \mathrm{d}x \mathrm{d}y = 1, \end{cases} \tag{2.22}$$

with same boundary condition as in equation (2.20). We aslo solve Fokker-Planck equation (2.12) with normal distribution $N(60, 1)$ as an initial condition for chemical system (2.1). We refer to [Hoffman (2001)] for any details about numerical methods for partial differential equation.

2.2.4 Comparison of the Methods

Contrary to the Monte Carlo method in Section 2.2.2 we can easily obtain smooth solutions $p(t, \mathbf{x})$ using the Fokker-Planck equation also for time dependent problems. Many trajectories with Gillespie's method are needed for an accurate estimate of the time dependent probability. It is more difficult to decide when to stop the Monte Carlo simulation. The main advantage of Gillespie's algorithm is its ability to treat systems with large dimension N and number of reactions M. It needs only $N + 2M$ memory locations for a simulation whereas numerical solution of the Fokker-Planck equation with a traditional grid based method is limited to $N = 5$ or perhaps 6. When N is small it is, however, very competitive. In an example in [Sjöoberg, et al. (2009)] with $M = 2$ the steady state solution is obtained with the solver of the Fokker-Planck equation 130 times faster than with Gillespie's algorithm [Sjöoberg, et al. (2009)]. If the statistics is collected for p with the Monte Carlo method and there are $x_{\max}$ molecules of each species, then also that method needs $x^N_{\max}$ storage.

2.3 Numerical Results of Particular Methods

In this section, we use the MATLAB language to program three types of numerical computations. First, we program the Gillespie's stochastic simulation, then we compute the solution to the system of ordinary equations and the dynamic solution to Fokker Planck equation. We apply these methods to the two types of chemical system. We start with an analysis of the one-dimensional chemical switch (2.2). We use such bifurcation parameters for which the stochastic chemical system has two equilibria. Then we also apply these methods to the synthesis of two metabolites (2.5).

2.3.1 One Dimensional Switch System

Let $X(t)$ be the number of molecules of the chemical X. The deterministic description of chemical system (2.1) is given by the mean field of ordinary differential equations (2.2) for concentration $x(t) = \frac{X(t)}{V}$, where V stands for the volume of the reactor. To obtain the stochastic description, we scale the rate constants with the appropriate powers of the volume V in the following manner:

$$\lambda_1 = \lambda_1 V, \qquad \lambda_2 = \frac{\lambda_2}{V}, \qquad \mu_1 = \mu_1, \qquad \mu_2 = \frac{\mu_2}{V^2}. \tag{2.23}$$

Now, we define the propensity functions of chemical reactions (2.1), which are used in Gillespie's stochastic simulation. Propensity functions for chemical system (2.1) are given by

$$\begin{aligned} &\alpha_1(x) = \lambda_1, \qquad \alpha_2(x) = \mu_1 x, \\ &\alpha_3(x) = \lambda_2 x(x-1), \qquad \alpha_4(x) = \mu_2 x(x-1)(x-2). \end{aligned} \tag{2.24}$$

Given the propensity functions (2.26), we can use the Gillespie's stochastic simulation algorithm from Section 2.2.2 to simulate the time evolution of system (2.1). The comparison of the time evolution of X given by the deterministic model (2.2) and by the Gillespie's simulation can be seen in Figure 2.1. We apply the same initial condition $X(0) = 0$ and the same parameter values (2.3) for both the stochastic and deterministic simulations. The reactor volume is V = 1. In the limit $V \to \infty$ (which is the so-called thermodynamic limit **?**), the stochastic description converges to the ordinary differential equations model 2.2; i.e., the probability distributions become Dirac and their expected value $\mathbb{E}X(t) \longrightarrow X$ as $V \to \infty$ converge to the solution to the ordinary differential equation (2.2). We can also achieve these results by solving the Fokker-Planck equation (2.12). The solution to the Fokker-Planck equation is in fact the time evolution of probability distribution $p(t, x)$. Figure 2.2 illustrates the evolution of probability distribution $p(t, x)$ for chemical system (2.1). In the picture on the left, Figure 2.2, we present snapshots of the probability evolution $p(t, x)$ in the initial state, and after 2 and 3 minutes. The distribution $p(x, t)$ of chemical system (2.1) drifts towards the right, which corresponds well to the formulation of chemical system (2.1). In the right Figure (2.2), we can see snapshots of the probability evolution $p(t, x)$ after 6,7 and 9 minutes. The distribution $p(t, x)$ of chemical system (2.1) goes rapidly to the right.

2.3.2 Synthesis of Two Metabolites

Let us consider two chemical species X and Y which are in a reactor of volume V and which are subjected to a set of four chemical reactions (2.4). Let $X(t)$ and $Y(t)$ be the number of

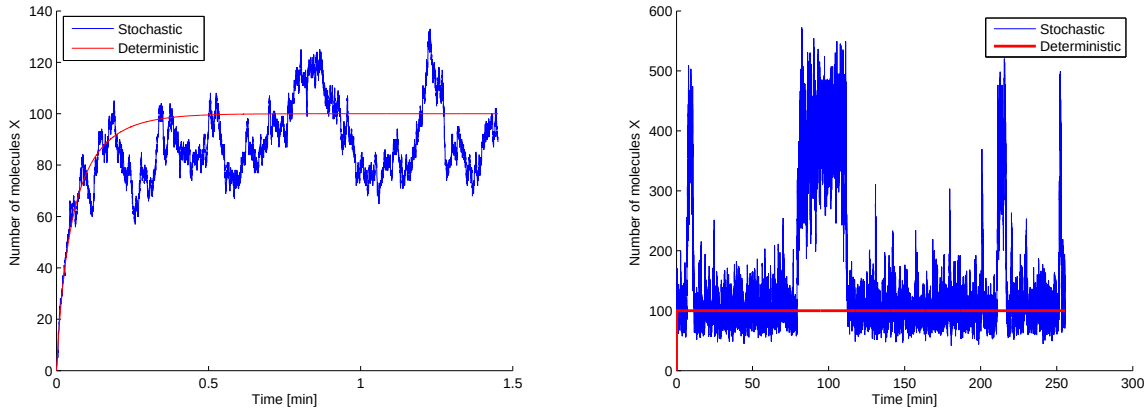

Figure 2.1: *One of the realizations of the stochastic simulation algorithm from Section 2.2.2 for system of chemical reactions (2.1) (blue line) and the solution to the deterministic ordinary differential equation (2.2) (red line).* (Left:) *The number of molecules of X as a function of time over the first* 90 *seconds of simulation. (Right:) Time evolution over* 260 *minutes.*

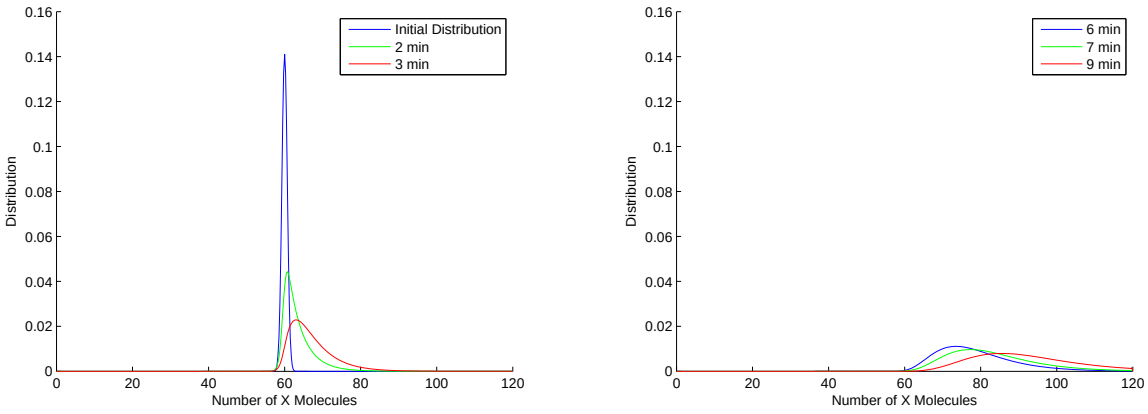

Figure 2.2: *A solution to the one dimensional Fokker Planck equation (2.12) of chemical system (2.1) with coefficients $k_1 = 3.1$, $k_2 = 2 \times 10^{-2}$, $k_3 = 3 \times 10^{-5}$ and $k_4 = 1.9 \times 10^{-8}$, with both the drift and the diffusion term.* (Left:) *The snapshots of the probability evolution $p(t, x)$ in the initial state, and after* 2 *and* 3 *minutes.* (Right:) *The snapshots of the probability evolution $p(t, x)$ after* 6, 7 *and* 9 *minutes.*

molecules of the chemical species X and Y, respectively. The concentration of X (resp., Y) will be denoted by $x = \frac{X}{V}$ (resp., $y = \frac{Y}{V}$). In order to be able to describe the time evolution of x and y by the mean-field ordinary differential equations (2.5), we need to have enough molecules of X and Y in the system and they ought to be well-mixed. Then the stochastic model of the chemical system (2.4) can be obtained using the Gillespie's stochastic algorithm from Section 2.2.2. As a matter of fact, this is equivalent to solving the master equation (2.7) that corresponds to this problem (2.7). Again, we scale the rate constants with the appropriate power of the volume V as seen below:

$$\lambda_1 = \mu_1, \qquad \lambda_2 = \mu_2, \qquad \lambda_1 = \lambda_1 V, \qquad \lambda_2 = \lambda_2 V. \tag{2.25}$$

Then we multiply the number of the molecules available for reaction and the scaled rate constants to obtain the propensity functions of the reactions in question, in particular:

$$\alpha_1(x,y) = \mu_1 x(x-1), \quad \alpha_2(x,y) = \mu_2 xy, \quad \alpha_3(x,y) = \lambda_1, \quad \alpha_4(x,y) = \lambda_2. \tag{2.26}$$

Using the equation of ordinary differential system (2.5) and the Gillespie's algorithm from Section 2.2.2, we can simulate the stochastic trajectories of (2.4). We apply initial condition $[X(0), Y(0)] = [0, 0]$ and the same parameter values (2.6) for both the stochastic and deterministic simulations. In Figure (2.3.2), we compare the stochastic and deterministic time evolution of chemical X given by Gillespie's algorithm from Section 2.2.2 and solution of ordinary differential equations (2.2) respectively. In the picture on the left in Figure (2.3.2) we can see a short simulation of the time evolution of chemical X. The one on the right in Figure (2.3.2) plots a longer simulation after 35000 minutes of the time evolution of chemical X. In Figure 2.3.2, we compare the time evolution of Y given by the stochastic Gillespie's

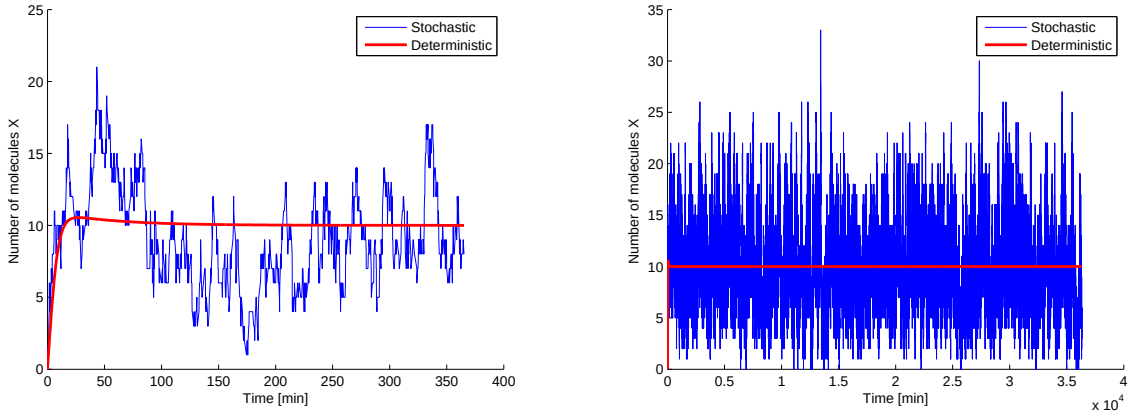

Figure 2.3: *One of the realizations of the Gillespie's stochastic simulation algorithm from Section 2.2.2 for the system of chemical reactions (2.4) (blue line) and the solution to the deterministic ordinary differential equation (2.5) (red line). (Left) The number of molecules of X as a function of time over the first* 360 *minutes of simulation.* (Right:) *Time evolution over* 35000 *minutes.*

algorithm described in Section 2.2.2 and the deterministic (2.5) models.

We can also achieve the same results by solving the partial differential equation (2.20) with the same parameters (2.6). Solution to the partial differential equation (2.20) is again the time evolution of probability distribution $p(t, x, y)$. Figure 2.2 shows the evolution of probability distribution $p(t, x)$ for chemical system (2.1). In the left picture of Figure 2.5, we can see the snapshots of the probability evolution $p(t, x, y)$ after 1 minute. The picture on the right in the same figure depicts the time evolution of probability distribution $p(t, x, y)$ after 2 minutes. In both Figures (2.5) we can see that the evolution of $p(t, x, y)$ drifts to the right. We can notice that this corresponds well to the formulation of chemical system (2.4). The snapshot of the time evolution of $p(t, c, y)$ after 5 and 10 minutes is depicted in the last Figure (2.6)

We can visually compare the time evolution of chemical X in 1, 2, 5 and 10 minutes, that was obtained as a solution to the Fokker-Planck equation (2.20) illustrated in Figure (2.5) and Figure (2.6), with the short simulation depicted in the left picture of Figure 2.3.2 and the left

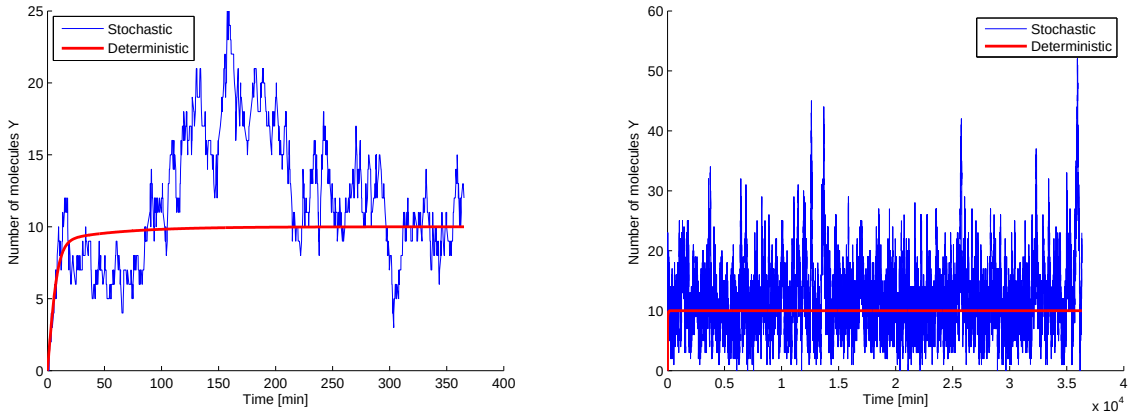

Figure 2.4: *One of the realizations of chemical Y of Gillespie's stochastic simulation algorithm from Section (2.2.2) for the system of chemical reactions (2.4) (blue line) and the solution to the ordinary differential equations (2.5) (red line).* (Left:) *The number of molecules of Y as a function of time over the first* 360 *minutes of simulation.* (Right:) *Time evolution over* 35000 *minutes.*

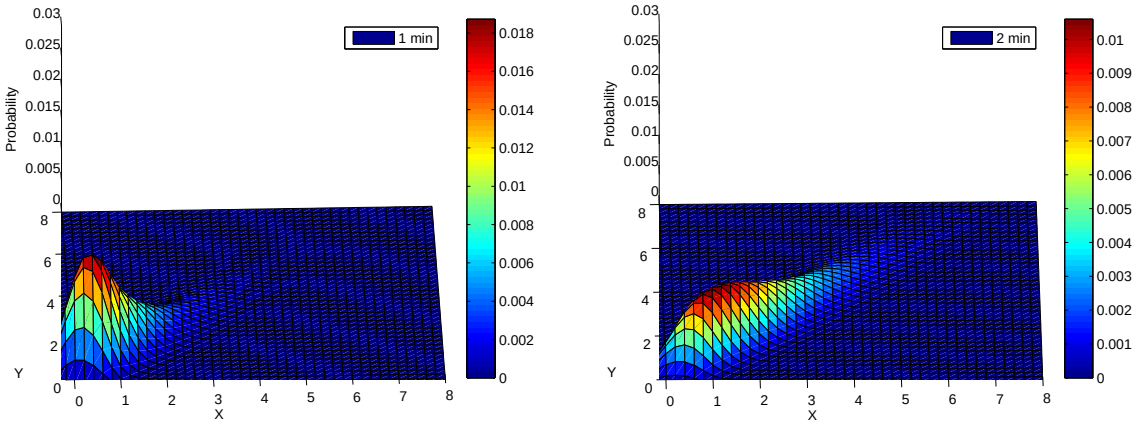

Figure 2.5: *The solution to Fokker-Planck equation (2.20), restricted to the subdomain $(0,8) \times (0,8)$, and computed by the finite difference method from Section 2.2.3. We use parameter values from (2.6).* (Left:) *The snapshot after one minute of the evolution of probability distribution $p(t,x,y)$.* (Right:) *The snapshot after two minutes of the evolution of probability distribution $p(t,x,y)$.*

picture of Figure 2.3.2. The time evolution of probability distribution $p(t,x,y)$ corresponds to the stochastic simulation from Section (2.2.2) and the solutions to the system of deterministic equations (2.5).

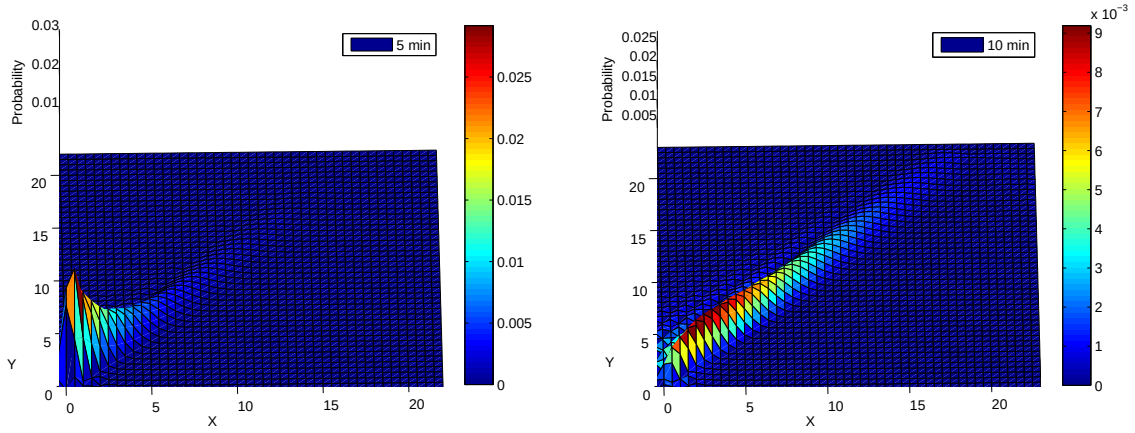

Figure 2.6: *The solution to Fokker-Planck equation (2.20), restricted to the subdomain* $(0, 23) \times (0, 23)$*, and computed by the finite difference method from Section 2.2.3. We use parameter values (2.6).* (Left:) *The snapshot after five minutes of the evolution of probability distribution* $p(t, x, y)$*.* (Right:) *The snapshot after ten minutes of the evolution of probability distribution* $p(t, x, y)$*.*

Chapter 3

Ergodic Solution

There are two main aims in cell biology. The first one is to compute the probability $p(t_0, \boldsymbol{\varphi}, t, \boldsymbol{x})$ that $\boldsymbol{X}(t) = \boldsymbol{x}$, i.e., the probability that there are $\boldsymbol{x}$ molecules of the chemical species $\boldsymbol{X}$ at time t in the system. The second one is to compute the stationary distribution $\rho_S(\boldsymbol{x}) = \lim_{t\to\infty} p(\cdot, t, \boldsymbol{A})$ of chemical species $\boldsymbol{X}$ in the chemical system. Stochastic chemical systems are often described by the equation:

$$\mathrm{d}\boldsymbol{X} = \boldsymbol{b}(t, \boldsymbol{X})\mathrm{d}t + \sqrt{2\boldsymbol{\sigma}(t, \boldsymbol{X})}\mathrm{d}\boldsymbol{W}, \quad \boldsymbol{X}(t_0) = \boldsymbol{\varphi}. \tag{3.1}$$

where $\boldsymbol{W}$ is n-dimensional $(\mathcal{F}_t)$-Wiener process, $\boldsymbol{b}(t, \boldsymbol{X})$ is a drift coefficient, $\boldsymbol{\sigma}(t, \boldsymbol{X})$ is a diffusion coefficient and $\boldsymbol{\varphi}$ is an initial condition. In order to compute the transition probability $P(t_0, \boldsymbol{\varphi}, t, \boldsymbol{A})$ it is necessary to check if the solution to equation (3.1) can be expressed as an Markov process $bX^{t_0,\boldsymbol{\varphi}}$. Then, after verifying the condition of existence invariant measure $\mathrm{P}_{S(\mathrm{d}\boldsymbol{x})}$ associated with the Markov process $\boldsymbol{X}^{t_0,\boldsymbol{\varphi}}$ under some restriction we compute the density of invariant measure $\rho_S(\boldsymbol{x})$ of chemical systems (2.1) and (2.4) see Figure 3.1 and Figure 3.2 respectively. In Section 3.2, we therefore give conditions implying the existence of stationary Markov process, stated in terms of the properties of the transition probability functions. Since one of the main conditions to the existence of an invariant measure is the requirement of regularity of the solution we also give conditions implying the regularity of the solution in Section 3.1. Then, we verify these conditions for one dimensional chemical switch in Section 3.3 and also for two dimensional chemical system in Section 3.3.2. For these two chemical systems we also compute numerically stationary distribution and compare them to stochastic simulations. We use Khasminskii (2011), Soize (1994), Strook (2005) and Seidler (2011) as main references.

3.1 The Regularity of the Solution

Notation.

(i) Let $\mathbf{W}(\cdot)$ be an n-dimensional Brownian motion. Let $(\Omega, \mathcal{F}, (\mathcal{F}_t), \mathrm{P})$ be a stochastic basis with filtration which complies with $\mathcal{F}_0 \supseteq \{N \in \mathcal{F}_\infty; \mathrm{P}(N) = 0\}$ and $\mathcal{F}_{t+} \equiv \bigcap_{v>t} \mathcal{F}_v$ for all $t \geq 0$.

(ii) Assume $T > 0$ is given, and $\boldsymbol{b} : [0, T] \times \mathbb{R}^m \to \mathbb{R}^m$ and $\boldsymbol{\sigma} : [0, T] \times \mathbb{R}^m \to \mathbb{R}^{m\times n}$ are given borel functions.

(iii) Let $\boldsymbol{\varphi} : \Omega \to \mathbb{R}^m$ be m-dimensional random variable which is independent of $\mathbf{W}(\cdot)$ and $t_0 \in [0, T]$.

(iv) $\exists K < \infty \ \forall t \in [0, T] \ \forall \boldsymbol{x}, \boldsymbol{y} \in \mathbb{R}^m$

$$\|\boldsymbol{b}(t, \boldsymbol{x}) - \boldsymbol{b}(t, \boldsymbol{y})\| \vee \|\boldsymbol{\sigma}(t, \boldsymbol{x}) - \boldsymbol{\sigma}(t, \boldsymbol{y})\| \leq K \|\boldsymbol{x} - \boldsymbol{y}\| . \tag{3.2}$$

(v) The integral

$$I(t) = \int_0^t \sigma(u) \mathrm{d}W(u) \tag{3.3}$$

means the Itô integral for integrand $\sigma(t)$. For more information about Itô integral see [Øksendal (2007)].

Before we introduce needed theorems to proofing regular solution to stochastic differential equation (3.7), we shortly introduce the main definitions of Markov process. This definition are needed to derive transition probability.

A stochastic process $X(t)$ with values in $\mathbb{R}^m$, defined for $t \geq 0$ on a probability space $(\Omega, \mathcal{F}, (\mathcal{F}_t), \mathrm{P})$, is called *Markov process* if, for all $\boldsymbol{A} \in \mathcal{B}$, $0 \leq s < t$,

$$\mathrm{P}\{\boldsymbol{X}(t) \in |\mathcal{N}_s\} = \mathrm{P}\{\boldsymbol{X}(t) \in \boldsymbol{A} | \boldsymbol{X}(s)\} \tag{3.4}$$

where $\mathcal{N}_s$ is the σ-algebra of events generated by the form

$$\{\boldsymbol{X}(u) \in \boldsymbol{A}\} \quad (u \leq s, \boldsymbol{A} \in \mathcal{B}).$$

There exist a function $P(s, \boldsymbol{x}, t, \boldsymbol{A})$, defined for $0 \leq s \leq t$, $\boldsymbol{x} \in \mathbb{R}^m$, $\boldsymbol{A} \in \mathcal{B}$, which is $\mathcal{B}$-measurable in $\boldsymbol{x}$ for every fixed s, t, $\boldsymbol{A}$ and which mean a measure as a function of the set $\boldsymbol{A}$, holding the condition

$$\mathrm{P}\{\boldsymbol{X}(t) \in \boldsymbol{A} | \boldsymbol{X}(s)\} = P(s, \boldsymbol{X}(s), t, \boldsymbol{A}). \tag{3.5}$$

We can also prove that for all $\boldsymbol{x}$, except from a set $\boldsymbol{B}$ such that $P\{\boldsymbol{x}(s) \in \boldsymbol{B}\} = 0$, the Chapman-Kolmogorov equation hold:

$$P\{s, \boldsymbol{x}, t, \boldsymbol{A}\} = \int_{R^m} P(s, \boldsymbol{x}, u, \mathrm{d}\boldsymbol{y}) P(u, \boldsymbol{y}, t, \boldsymbol{A}). \tag{3.6}$$

The function $P\{s, \boldsymbol{x}, t, \boldsymbol{A}\}$ is called the *transition probability function* of the Markov process. We say that the transition probability function $P(s, \boldsymbol{x}, t, \boldsymbol{A})$ is *time-homogeneous* if the function $P(s, \boldsymbol{x}, t + s, \boldsymbol{A})$ is independent of s. We use notation $P(s, \boldsymbol{x}, t, \boldsymbol{A}) = P(\boldsymbol{x}, t, \boldsymbol{A})$ for time-homogeneous transition probability function.

In the following text, we introduce needed definitions and theorems about regularity solution.

Definition 3.1.1. We say that a pair $(\mathbf{X}, \tau)$ is a local solution to the Itô stochastic differential equation

$$\mathrm{d}\boldsymbol{X} = \boldsymbol{b}(t, \boldsymbol{X})\mathrm{d}t + \boldsymbol{\sigma}(t, \boldsymbol{X})\mathrm{d}\boldsymbol{W}, \quad \boldsymbol{X}(t_0) = \boldsymbol{\varphi} \tag{3.7}$$

if

(i) $\tau : \Omega \to]t_0, \infty]$ is a markov time,

(ii) $\boldsymbol{X} : [t_0, \tau[\to \mathbb{R}^m$ is progressively measurable,

(iii) $\limsup_{t \nearrow \epsilon(\omega)} \|\boldsymbol{X}(t,\omega)\| = +\infty$ for all $\omega \in \Omega$ such that $\epsilon(\omega) < \infty$,

(iv) there exists a sequence of Markov times η^N, $N \in \mathbb{N}$, for which $t_0 \leq \eta^N < \tau$ and, $\eta^N \nearrow \tau$ holds, such that

$$\boldsymbol{X}(t \wedge \eta^N) = \boldsymbol{\varphi} + \int_{t_0}^{t \wedge \eta^N} \boldsymbol{b}(s, \boldsymbol{X}(s))\mathrm{d}s + \int_{t_0}^{t \wedge \eta^N} \boldsymbol{\sigma}(s, \boldsymbol{X}(s))\mathrm{d}\boldsymbol{W}(s) \tag{3.8}$$

for all $t \geq t_0$.

We call the Markov time τ the explosion time of the solution $\boldsymbol{X}(\cdot)$.

Theorem 3.1.2 (Existence and Uniqueness)**.** Suppose that $\boldsymbol{b} : [0,T] \times \mathbb{R}^m \to \mathbb{R}^m$ and $\boldsymbol{\sigma} : [0,T] \times \mathbb{R}^m \to \mathbb{R}^{m \times n}$ are continuous and satisfy the following conditions:

(I) $\forall N \in \mathbb{N}\ \exists K_N < \infty\ \forall t \geq 0\ \forall \boldsymbol{x},\boldsymbol{y} \in \mathbb{R}^m,\ \|\boldsymbol{x}\| \vee \|\boldsymbol{y}\| \leq N$

$$\|\boldsymbol{b}(t,\boldsymbol{x}) - \boldsymbol{b}(t,\boldsymbol{y})\| \vee \|\boldsymbol{\sigma}(t,\boldsymbol{x}) - \boldsymbol{\sigma}(t,\boldsymbol{y})\| \leq K_N \|\boldsymbol{x} - \boldsymbol{y}\|,$$

(II) $\sup_{t \geq 0}\{\|\boldsymbol{b}(t,\boldsymbol{0})\| + \|\boldsymbol{\sigma}(t,\boldsymbol{0})\|\} \equiv K^* < \infty.$

(III) Let $\boldsymbol{\varphi} : \Omega \to \mathbb{R}^m$ be a m-dimensional random variable which is independent of the σ-algebra $\mathcal{F}_\infty$ generated by $W_s(\cdot)$, $s \geq 0$ such that $\mathbb{E}|\boldsymbol{\varphi}|^2 < \infty$.

Then there exists a unique solution $(\boldsymbol{X}, \tau)$ to the stochastic differential equation in (3.7). Moreover, if the following condition is satisfied:

(IV) $\exists K_* < \infty\ \forall t \geq 0\ \forall \boldsymbol{x} \in \mathbb{R}^m$

$$\|\boldsymbol{b}(t,\boldsymbol{x})\| \vee \|\boldsymbol{\sigma}(t,\boldsymbol{x})\| \leq K_*(|1 + \|\boldsymbol{x}\|),$$

then $\tau = +\infty$ almost surely.

Remark 3.1. (i) **Uniqueness** means that if $(\boldsymbol{X}, \tau\boldsymbol{X})$ and $(\boldsymbol{Y}, \tau\boldsymbol{Y})$, have almost surely continuous sample paths, and both locally solve (3.7) and almost surely satisfy $\boldsymbol{X}(t_0) = \boldsymbol{Y}(t_0)$, then $\tau\boldsymbol{X} = \tau\boldsymbol{Y}$ almost surely and

$$\mathrm{P}\{\omega \in \Omega; \boldsymbol{X}(t,\omega) = \boldsymbol{Y}(t,\omega) \quad \forall t \in [t_0, \tau\boldsymbol{X}(\omega)[\} = 1.$$

(ii) Hypothesis (I) says that $\boldsymbol{b}$ and $\boldsymbol{\sigma}$ are **uniformly Lipschitz continuous** in the variable $\boldsymbol{x}$.

The condition of linear growth (IV) is often a too restrictive in applications. Moreover, in the cell biology most chemical systems do not satisfy condition (IV). Therefore, we present more general, but sufficient conditions for regularity. Let τ denote the limit of the monotone increasing sequence τ_n as $n \to \infty$.
We say that process $\boldsymbol{X}(t)$ is **regular** if for any $s \in [0,T]$ and $\boldsymbol{x} \in \mathbb{R}^m$

$$\mathrm{P}^{s,\boldsymbol{x}}\{\tau = \infty\} = 1. \tag{3.9}$$

For any $V \in C^{1,2}$, we define a function $LV : \mathbb{R}_+ \times \mathbb{R}^m \to \mathbb{R}$ as

$$LV(t,\boldsymbol{x}) = \frac{\partial V(t,\boldsymbol{x})}{\partial t} + \sum_{i=1}^{m} b_i(t,\boldsymbol{x})\frac{\partial V(t,\boldsymbol{x})}{\partial x_i} + \frac{1}{2}\sum_{i,j=1}^{m} a_{i,j}(t,\boldsymbol{x})\frac{\partial^2 V(t,\boldsymbol{x})}{\partial x_i \partial x_j}. \tag{3.10}$$

where $t \geq 0$ and $\boldsymbol{x} \in \mathbb{R}^m$ and $a(t,\boldsymbol{x}) \equiv \sigma(t,\boldsymbol{x})\sigma(t,\boldsymbol{x})^T$. The operator L defined by (3.10) is called the generator of Markov process. The probabilistic meaning of the operator L for any function $V \in C^2$ is given by following lemma:

Lemma 3.1.3. Let $\boldsymbol{X}(u)$ be a process satisfying (3.8) on the time interval $[s,T]$, $V \in C^2$, τ_U the random variable equal to the time at which the function of the process $\boldsymbol{X}(u)$ first leaves the bounded neighborhood U, and let $\tau_U(t) = \min(\tau_U, t)$. Suppose moreover that $\mathrm{P}\{\boldsymbol{X}(s) \in U\} = 1$. Then

$$\mathbb{E}[V(\tau_U(t), \boldsymbol{X}(\tau_U(t))) - V(s, \boldsymbol{X}(s))] = \mathbb{E}\int_s^{\tau_U(t)} LV(u,\boldsymbol{X})\mathrm{d}u. \tag{3.11}$$

Proof. The process $\boldsymbol{Y}(t) = \boldsymbol{X}(\tau_U)$, obtained by stopping the process $\boldsymbol{X}(t)$ at the instant it reaches the boundary of the domain U, has an Itô differential:

$$\mathrm{d}\boldsymbol{Y}(t) = \mathbb{1}_{\{\tau_U > t\}}(\omega)\boldsymbol{b}(t,\boldsymbol{Y}(t))\mathrm{d}t + \mathbb{1}_{\{\tau_U > t\}}(\omega)\boldsymbol{\sigma}(t,\boldsymbol{Y}(t))\mathrm{d}W(t).$$

Applying the Ito formula to the process $\boldsymbol{Y}(t)$ and the function V, we get

$$V(\tau_U(t), \boldsymbol{X}(\tau_U(t))) - V(s,\boldsymbol{X}(s)) = \int_s^{\tau_U(t)} LV\,\mathrm{d}u + \sum_{i=1}^{n}\int_s^{\tau_U(t)} \boldsymbol{\sigma}_i\frac{\partial V}{\partial x_i}\mathrm{d}W(u). \tag{3.12}$$

We denote

$$\int_s^{\tau_U(t)} \boldsymbol{\theta}\mathrm{d}W(u) = \int_s^t \mathbb{1}_{\{\tau_U > t\}}(\omega)\boldsymbol{\theta}\mathrm{d}W(u). \tag{3.13}$$

The equation (3.13) and martingale property of stochastic integral imply (3.11). □

Theorem 3.1.4 (Khasminskii Test of Explosion)**.** Suppose that for equation (3.7) the conditions (I) and (II) of Theorem (4.3.1) hold and that there exists a function $V \in C^{1,2}$ such that

(i) $V \geq 0$ on $[t_0,\infty) \times \mathbb{R}^m$,

(ii)
$$V_R = \inf_{t \geq t_0, \|\boldsymbol{x}\| \geq R} V(t,\boldsymbol{x}) \to \infty \quad \text{as} \quad R \to \infty, \tag{3.14}$$

(iii) $\mathbb{E}V(t_0,\boldsymbol{\varphi}) < \infty$,

(iv) for some constant $c \geq 0$
$$LV(t,\boldsymbol{x}) \leq cV(t,\boldsymbol{x}) \quad \text{for all} \quad t \geq t_0 \quad \text{and} \quad \boldsymbol{x} \in \mathbb{R}^m. \tag{3.15}$$

Then the following statements hold:

1. $\mathrm{P}\{\tau = +\infty\} = 1$.

2. There exists a solution $\boldsymbol{X}(t)$ to (3.7) which is an almost surely continuous stochastic process and it is unique up to equivalence.

3. This solution is a Markov process whose transition probability function $P(t_0, \boldsymbol{\varphi}, t, \boldsymbol{A})$ is defined for $t > t_0$ by the relation $P(t_0, \boldsymbol{\varphi}, t, \boldsymbol{A}) = \mathrm{P}\{\boldsymbol{X}^{t_0,\boldsymbol{\varphi}}(t) \in \boldsymbol{A}\}$, where $\boldsymbol{X}^{t_0,\boldsymbol{\varphi}}(t)$ is a solution to the equation

$$\boldsymbol{X}^{t_0,\boldsymbol{\varphi}}(t) = \boldsymbol{\varphi} + \int_{t_0}^{t} \boldsymbol{b}(s, \boldsymbol{X}^{t_0,\boldsymbol{\varphi}}(s))\mathrm{d}s + \int_{t_0}^{t} \boldsymbol{\sigma}(s, \boldsymbol{X}^{t_0,\boldsymbol{\varphi}}(s))\mathrm{d}\boldsymbol{W}(s) \tag{3.16}$$

4. $\mathbb{E}V(t, \boldsymbol{X}(t)) \le \mathrm{e}^{(t-t_0)}\mathbb{E}V(t_0, \boldsymbol{\varphi}), \quad t \le t_0.$

Proof. We first prove that under the assumptions (3.14) and (3.15) the process $\widetilde{\boldsymbol{X}}(t) = \boldsymbol{X}_n$ for $t < \tau_n$ is regular. From 3.15 it follows that the function

$$W(t, \boldsymbol{x}) = V(t, \boldsymbol{x}) \exp\{-c(t - t_0)\}$$

satisfied $LW \le 0$. Hence by Lemma 3.1.3, for $\tau_n(t) = \min(\tau_n, t)$, we have

$$\begin{aligned}&\mathbb{E}\{V(\tau_n(t), \boldsymbol{X}(\tau_n(t))) \exp[-c(\tau_n(t) - t_0)]\} - \mathbb{E}V(t_0, \boldsymbol{X}(t_0))\\ &= \mathbb{E}\int_{t_0}^{\tau_n(t)} LW(u, \boldsymbol{X}(u))\mathrm{d}u \le 0.\end{aligned}$$

This, together with the inequalities $\tau_n \le t$, $V \ge 0$, implies

$$\mathbb{E}V(\tau_n(t), \widetilde{\boldsymbol{X}}(\tau_n(t))) \le \mathrm{e}^{c(t-t_0)}\mathbb{E}V(t_0, \boldsymbol{X}(t_0)). \tag{3.17}$$

From (3.17) we derive the estimate

$$\mathrm{P}\{\tau_n \le t\} \le \frac{\mathrm{e}^{c(t-t_0)}\mathbb{E}V(t_0, \widetilde{\boldsymbol{X}}(t_0))}{\inf_{|\boldsymbol{x}|>n, u>t_0} V(u, \boldsymbol{x})}.$$

Letting $n \to \infty$ and making use of (3.14), we now get (3.9); thus the process $\widetilde{\boldsymbol{X}}(t)$ is a solution of (3.8) for all $t \ge t_0$. This solution is unique up to equivalence. Indeed, it follows from the definition of $\widetilde{\boldsymbol{X}}(t)$ and from the uniqueness of the solution of (3.8) in the domain $|\boldsymbol{x}| < n$ that for every pair of solutions $\boldsymbol{X}(t)$ and $\boldsymbol{Y}(t)$

$$\mathrm{P}\Big\{\sup_{0<t<\tau_n} |\boldsymbol{X}(t) - \boldsymbol{Y}(t)| > 0\Big\} = 0. \tag{3.18}$$

All other properties of the process just constructed can be proved in a similar manner. □

3.2 The Invariant Measure of the Solution

Definition 3.2.1 (Invariant Measure and Steady State Density)**.** If there exists a probability measure $\mathrm{P}_S(\mathrm{d}\boldsymbol{x})$ on $\mathbb{R}^m$ independent of time t, as a solution to the integral equation

$$\forall t > 0, \qquad \mathrm{P}_s(\mathrm{d}\boldsymbol{y}) = \int_{\boldsymbol{x}\in\mathbb{R}^m} \mathrm{P}_S(\mathrm{d}\boldsymbol{x})P(\boldsymbol{x}; t, \mathrm{d}\boldsymbol{y}), \tag{3.19}$$

then, $\mathrm{P}_S(\mathrm{d}\boldsymbol{x})$ is called an *invariant measure* associated with Markov process $\boldsymbol{X}$. If $\mathrm{P}_S(\mathrm{d}\boldsymbol{x}) = \rho_S(\boldsymbol{x})\mathrm{d}\boldsymbol{x}$ has a density with respect to the Lebesgue measure $\mathrm{d}\boldsymbol{x}$ in $\mathbb{R}^m$, probability density function $\rho_S(\boldsymbol{x})$ is called *steady state probability density function.*

Theorem 3.2.2 (A Condition for the Existence of a Stationary Markov Process)**.** A necessary and sufficient condition for the existence of a stationary Markov process with the given time-homogeneous stochastically continuous transition probability function $P(\boldsymbol{\varphi}, t, \boldsymbol{A})$ is that for some point $\boldsymbol{\varphi} \in \mathbb{R}^m$

$$\lim_{R\to\infty} \lim_{T\to\infty} \inf \int_0^T P(\boldsymbol{\varphi}, t, U_R^c)\mathrm{d}t = 0, \tag{3.20}$$

where $U_R^c = \{\|x\| > R\}$.

Proof. See [Khasminskii (2011), Theorem 3.1.]. □

Unfortunately, the transition probability functions of complex processes, which we encounter in cell biology are usually not expressible in terms of the coefficients of the equation. Therefore, we show more applicable conditions for the existence of the invariant distribution.

Theorem 3.2.3 (The Existence of the Stationary Markov Process)**.** Suppose that the coefficients of (3.7) are independent of t and satisfy condition (4.10) in U_R for every $R > 0$, and that there exists a function $V(\boldsymbol{x}) \in C(\mathbb{R}^m)$ with properties

$$V(\boldsymbol{x}) \geq 0. \tag{3.21}$$

$$\sup_{\|x\|>R} LV(\boldsymbol{x}) = -A_R \to -\infty \quad \text{as} \quad R \to \infty. \tag{3.22}$$

Suppose, moreover, that the process $\boldsymbol{X}^{\boldsymbol{\varphi}}(t)$ is regular for at least one $\boldsymbol{\varphi} \in \mathbb{R}^m$. Then there exists a solution to (3.7) which is a stationary Markov process.

Proof. Let $\boldsymbol{X}^{\boldsymbol{\varphi}}(t)$ be a regular solution of (3.8) and let $V(\boldsymbol{x})$ satisfy conditions (3.21) and (3.22). Lemma (3.1.3) implies that

$$\mathbb{E}V(\boldsymbol{X}^{\boldsymbol{\varphi}}(\tau_n(t))) - V(\boldsymbol{x}) = \mathbb{E}\int_0^{\tau_n(t)} LV(\boldsymbol{X}^{\boldsymbol{\varphi}}(u))\mathrm{d}u.$$

As before. we denote $\tau_n = \inf\{t : |\boldsymbol{X}^{\boldsymbol{\varphi}}(t)| > n\}$, $\tau_n(t) = \min(\tau_n, t)$. Estimating the right hand side of this equality by means of the inequality

$$LV(\boldsymbol{X}^{\boldsymbol{\varphi}}(u)) \leq -\mathbb{1}_{|\boldsymbol{X}^{\boldsymbol{\varphi}}(u)|>R}(\omega)A_R + \sup_{\boldsymbol{x}\in\mathbb{R}^m} LV(\boldsymbol{x}),$$

we get

$$A_R\mathbb{E}\int_0^{\tau_n(t)} \mathbb{1}_{|\boldsymbol{X}^{\boldsymbol{\varphi}}(u)|>R}(\omega)\mathrm{d}u \leq c_1 t + c_2.$$

Since the process $\boldsymbol{X}^{\boldsymbol{\varphi}}(t)$ is regular, it follows that almost surely $\tau_n(t) \to t$ as $n \to \infty$. Letting $n \to \infty$ and then changing the order of integration in the last inequality, we obtain

$$\frac{1}{t}\int_0^t P(\boldsymbol{\varphi}, u, U_R^c)\mathrm{d}u < \frac{c_2}{A_R}. \tag{3.23}$$

It follows from (3.22) and (3.23) and Theorem 3.2.2 holds provided that there exist a stationary initial distribution. The solution of (3.8) with this initial distribution is obviously stationary. □

We use the following proposition (3.2.4) to compute the density of invariant measure $\rho_S(\boldsymbol{x})$ for ordinary chemical systems.

Proposition 3.2.4. (Steady State Fokker-Planck Equation for the Steady State Probability Density Function). Suppose that diffusion process $\boldsymbol{X}$ satisfies the following hypothesis:

i. Drift vector $\boldsymbol{b}(\boldsymbol{x}) \in \mathbb{R}^m$ and diffusion matrix $\boldsymbol{\sigma}(\boldsymbol{x}) \in R^{m\times n}$ of diffusion process $\boldsymbol{X}$ are independent on t. Then the transition probabilities are homogeneous, i.e. for all $0 \leq s < t < \infty$, $P(s, \boldsymbol{x}, t, \mathrm{d}\boldsymbol{y}) = P(\boldsymbol{x}, t-s, \mathrm{d}\boldsymbol{y})$.

ii. For all $t > 0$ and for all $\boldsymbol{x}$ in $\mathbb{R}^m$, homogeneous transition probability $P(\boldsymbol{x}, t, \mathrm{d}\boldsymbol{y}) = \rho(\boldsymbol{x}, t, \boldsymbol{y})\mathrm{d}\boldsymbol{y}$.

iii. Function $\boldsymbol{x} \mapsto \boldsymbol{b}(\boldsymbol{x})$ and $\boldsymbol{x} \mapsto \boldsymbol{\sigma}(\boldsymbol{x})$ are continuous on $\mathbb{R}^m$.

Moreover, if the function $\boldsymbol{x} \mapsto \rho_S(\boldsymbol{x})$ from $\mathbb{R}^m$ into $\mathbb{R}$ is the solution to the steady state Fokker-Planck equation which can be written for all $\boldsymbol{x}$ in $\mathbb{R}^m$ as

$$-\sum_{j=1}^{m} \frac{\partial}{\partial x_j}(b_j(\boldsymbol{x})\rho_S(\boldsymbol{x})) + \frac{1}{2}\sum_{j,k=1}^{m} \frac{\partial^2}{\partial x_j \partial x_k}(\sigma_{jk}(\boldsymbol{x})\rho_S(\boldsymbol{x})) = 0, \tag{3.24}$$

with the positivity and normalization conditions

$$\rho_S(\boldsymbol{x}) \geq 0, \forall \boldsymbol{x} \in \mathbb{R}^m, \qquad \int_{R^m} \rho_S(\boldsymbol{x})\mathrm{d}\boldsymbol{x} = 1,$$

then $\mathrm{P}_S(\mathrm{d}\boldsymbol{x}) = \rho_S(\boldsymbol{x})$ is an invariant measure.

Proof. See [Soize (1994), Proposition 9.]. □

3.3 Stationary Distribution

We have two aims in this section. First, we want to verify that the computation of the transition probability function as a solution to the Fokker-Planck equation was correct in Chapter 2. Hence, we verify that the global solution $\boldsymbol{X}(t)$ exists and this solution is a Markov process $X^{s,x}$ with the transition probability function $P(s, \boldsymbol{x}, t, \boldsymbol{A})$. Then, we confirm that the invariant measure $\mathrm{P}_S(\boldsymbol{x})$ associated with the Markov process $\boldsymbol{X}^{s,x}$ exists. Afterwards, we can compute, with respect to any restriction, its density of invariant measure for chemical systems (2.1) and (2.4), mentioned in Chapter 2.

3.3.1 One-dimensional chemical switch

Let us consider the same one dimensional switch as in Chapter 2 which is subject to the following set of four reactions

$$\emptyset \xrightarrow{\lambda_1} X \xrightarrow{\mu_1} \emptyset \qquad 2X \xrightarrow{\lambda_2} 3X \xrightarrow{\mu_2} 2X. \tag{3.25}$$

The Langevin equation for chemical system (3.25) is

$$\mathrm{d}X = b(X)\mathrm{d}t + \sigma(X)\mathrm{d}W, \qquad X(t_0) = \varphi, \tag{3.26}$$

where the drift coefficient $b(x)$ and the diffusion coefficient $\sigma(x)$ are given by

$$b(x) = \lambda_1 - \mu_1 x + \lambda_2 x(x-1) - \mu_2 x(x-1)(x-2), \tag{3.27}$$

$$\sigma(x) = \begin{cases} \sqrt{\lambda_1 + \mu_1 x + \lambda_2 x(x-1) + \mu_2 x(x-1)(x-2)} & x \geq 0 \\ \sqrt{\lambda_1} & x < 0 \end{cases}$$

We verify conditions (3.1.4) for the existence of a regular solution which is a Markov process $X^{t_0,\varphi}$ with transition probability function $P(t_0, \varphi, t, A)$.

1. **Lipschitz condition**

   i. Function $\sigma(x)$ is square root of a polynomial for all $x \geq 0$. This polynomial is positive if the conditions $\lambda_2 > 3\mu_2$,$\mu_1 > \lambda_2$ and $\lambda_1 > 0$, $\lambda_2 > 0$, $\mu_1 > 0$ and $\mu_2 > 0$ hold. Therefore, $\sigma(x)$ is Lipschitz continuous in any compact subinterval of $[0, \infty)$.

   ii. Function $\sigma(x)$ is constant and therefore it is Lipschitz continuous for all $x < 0$.

   iii. Function $\sigma(x)$ is also continuous in the point $x = 0$ and therefore it is Lipschitz continuous on any compact subinterval of $\mathbb{R}$.

2. **Regular solution**
   We prove that our chemical system (3.25) described by Langevin equation (3.26) has a global solution. We choose Lyapunov function $V(x) = 1 + x^2$, $x \in \mathbb{R}$. Then $V \in C^2(\mathbb{R})$,$V > 0$ in $\mathbb{R}$ and

   $$V'(x) = 2x, \qquad V''(x) = 2, \qquad x \in \mathbb{R}.$$

   After applying operator L to function $V(x)$ we get

   $$\begin{aligned} LV(x) &= 2xb(x) + 2\sigma(x) = \\ &= 2\Bigg(\lambda_1 x - \mu_1 x^2 + \lambda_2 x^3 - \lambda_2 x^2 - \mu_2 x^4 + 3\mu_2 x^2 - \mu_2 x^2 + \\ &+ \frac{\lambda_1 + \mu_1 x + \lambda_2 x^2 - \lambda_2 x + \mu_2 x^3 - \mu_2 x + \mu_2 x}{2}\Bigg) \\ &= 2R(x), \qquad x \in \mathbb{R}. \end{aligned}$$

   The highest exponent is odd and its coefficient is negative. Therefore, we get the following function convergence

   $$\lim_{|x| \to \infty} R(x) = -\infty. \tag{3.28}$$

   Constant c can be derived by a simple adjustment as $c = \max(2\lambda_1 + \mu_1 + \mu_2, 2\lambda_2 + \mu_2)$. Therefore chemical system 3.25 has a regular solution.

Theorem 3.1.4 implies that the solution $X^{t_0,\varphi}(t)$ is a Markov process with transition probability function $P(t_0, \varphi, t, A)$. It is possible to prove that the transition probability function has a density with respect to the Lebesgue measure,

$$P(t_0, \varphi, t, A) = \int_A p(t_0, \varphi, t, z)\mathrm{d}z, \qquad s \in [0, T], \quad t \in [0, T], \quad \varphi \in \mathbb{R}^m, \quad A \in \mathcal{B}.$$

and function $p(\cdot,\cdot,t,z)$ solves the Fokker-Planck equation (2.11). Thus we verified that the computation of the transition probability function as a solution to the Fokker-Planck equation was correct. For the numerical solution see Figure 2.2.

3. **Invariant measure**
   We need to verify conditions (3.21) and (3.22). Condition (3.21) obviously holds. The validity of the second condition (3.22) follows from (3.28).

Given that our aim is to construct the density of invariant measure $\rho_S(\boldsymbol{x})$, we use Proposition 3.2.4. Figure 3.1 depicts the numerical solution to the stationary equation (3.24) with coefficients (2.3). We also simulate the density of invariant measure $\rho_S(\boldsymbol{x})$ by the Monte Carlo simulation from Section 2.2.2.

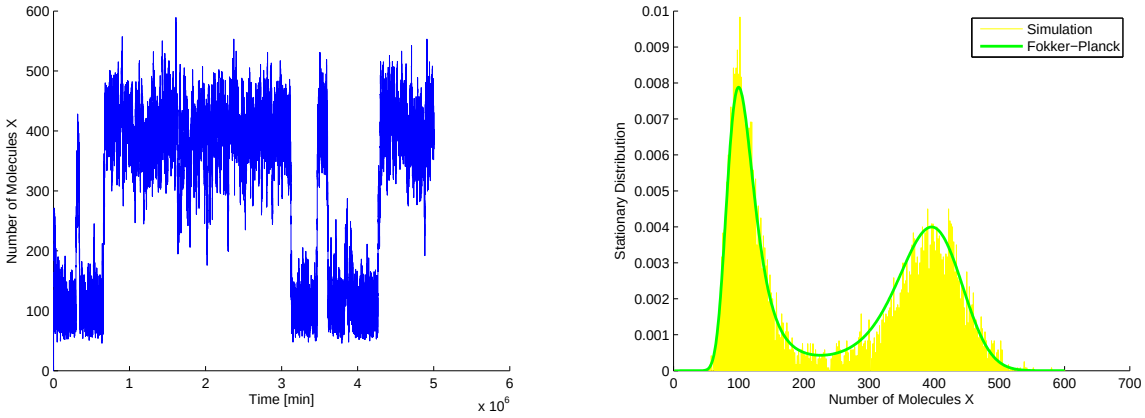

Figure 3.1: (Left:) *The time evolution of X, given by the stochastic models of the chemical system (2.1) at the interval $[0, 10^6]$.* (Right:) *Stationary distribution of (2.1) obtained by the Gillespie's stochastic simulation algorithm described in Section 2.2.2. The green line is the stationary solution (2.11) to the chemical Fokker-Planck equation.*

3.3.2 Synthesis of Two Metabolites

Let us consider chemicals X and Y, which are subjected to the following set of chemical reactions

$$X + X \xrightarrow{\mu_1} \emptyset \qquad X + Y \xrightarrow{\mu_2} \emptyset \qquad \emptyset \xrightarrow{\lambda_1} X \qquad \emptyset \xrightarrow{\lambda_2} Y. \tag{3.29}$$

This chemical system is the same as in Chapter 2. Let $A = \{[x,y] \in \mathbb{R}^2; x \geq 0, y \geq 0\}$ and $S = \{[x,y] \in \mathbb{R}^2\} \backslash A$ be the real sets. The Langevin equation for the chemical system (3.29) is

$$\mathrm{d}\boldsymbol{X} = \boldsymbol{b}(\boldsymbol{X})\mathrm{d}t + 2\boldsymbol{\sigma}(\boldsymbol{X})\mathrm{d}W, \qquad \boldsymbol{X}(t_0) = \boldsymbol{\varphi}, \tag{3.30}$$

where the drift and diffusion coefficients are given by

$$b_x(x,y) = \begin{cases} -\mu x(x-1) - \theta xy + \lambda_1 & [x,y] \in A \\ \lambda_1 & [x,y] \in S \end{cases}$$

$$b_y(x,y) = \begin{cases} -\theta xy + \lambda_2 & [x,y] \in A \\ \lambda_2 & [x,y] \in S \end{cases}$$

$$\sigma_x(x,y) = \begin{cases} \sqrt{\mu x(x-1) + \theta xy + \lambda_1} & [x,y] \in A \\ \lambda_2 & [x,y] \in S \end{cases}$$

$$\sigma_y(x,y) = \begin{cases} \sqrt{\theta xy + \lambda_2} & [x,y] \in A \\ \lambda_2 & [x,y] \in S \end{cases}$$

We verify conditions (3.1.4) for the existence of a regular solution which is a Markov process $\boldsymbol{X}^{t_0,\boldsymbol{\varphi}}$ with transition probability function $P(t_0, \boldsymbol{\varphi}, t, \boldsymbol{A})$.

1. **Lipschitz condition**

   (a) The Lipschitz condition for the all functions in any compact subinterval of A hold. We can prove it with the similar techniques as in the previous example in Section 3.3.1.

2. **Regular solution**
   We prove that our chemical system (3.29) described by Langevin equation (3.30) has a global solution. We choose Lyapunov function $V(x,y) = 1 + x^2 + y^2$, $[x,y] \in A$. Then $V \in C^2(\mathbb{R}^2)$, $V > 0$ in $\mathbb{R}^2$ and

   $$\frac{\partial V(x,y)}{\partial x} = 2x, \qquad \frac{\partial V(x,y)}{\partial y} = 2y, \qquad \frac{\partial V(x,y)}{\partial x \partial y} = 0, \qquad \frac{\partial V(x,y)}{\partial x^2} = 2, \quad \frac{\partial V(x,y)}{\partial y^2} = 2.$$

   After applying the operator L to the function $V(x,y)$ and simple modification of the following equation we get

   $$\begin{aligned} LV(x,y) &= 2xb_x(x,y) + 2yb_x(x,y) + 2\sigma_x(x,y) + 2\sigma_y(x,y) = \\ &= -2\mu x^3 + 3\mu x^2 + 2\lambda_1 x - 2\theta xy^2 + 2\lambda_2 y - \mu x + \lambda_1 \\ &= 2R(x,y) \qquad [x,y] \in A. \end{aligned}$$

   We get the following function convergence

   $$\lim_{||x|| \to \infty} R(x,y) = -\infty. \tag{3.31}$$

   For the functions define in the set S the regularity condition also hold. Therefore chemical system 3.29 has a regular solution.

Theorem 3.1.4 implies that the solution $\boldsymbol{X}^{t_0,\boldsymbol{\varphi}}(t)$ is a Markov process with transition probability function $P(t_0, \boldsymbol{\varphi}, t, \boldsymbol{A})$. It is possible to prove that the transition probability function has a density with respect to the Lebesgue measure,

$$P(t_0, \boldsymbol{\varphi}, t, \boldsymbol{A}) = \int_{\boldsymbol{A}} p(t_0, \boldsymbol{\varphi}, t, \boldsymbol{z}) \mathrm{d}\boldsymbol{z}, \qquad s \in [0,T], \quad t \in [0,T], \quad \boldsymbol{\varphi} \in \mathbb{R}^2, \quad \boldsymbol{A} \in \mathcal{B}.$$

and function $p(\cdot, \cdot, t, \boldsymbol{z})$ solves the Fokker-Planck equation (2.11). Thus we verified that the computation of the transition probability function as a solution to the Fokker-Planck equation was correct. For the numerical solution see Figure 2.5.

3. **Invariant measure**
   We need to verify conditions (3.21) and (3.22). Condition (3.21) obviously holds. The validity of the second condition (3.22) follows from (**??**).

Given that our aim is to construct the density of invariant measure $\rho_S(\boldsymbol{x})$, we use Proposition 3.2.4. Figure 3.2 depicts the numerical solution to the stationary equation (2.22) with coefficients (2.6). We also simulate the density of invariant measure $\rho_S(\boldsymbol{x})$ by the Monte Carlo simulation from Section 2.2.2, see Figure 3.3.

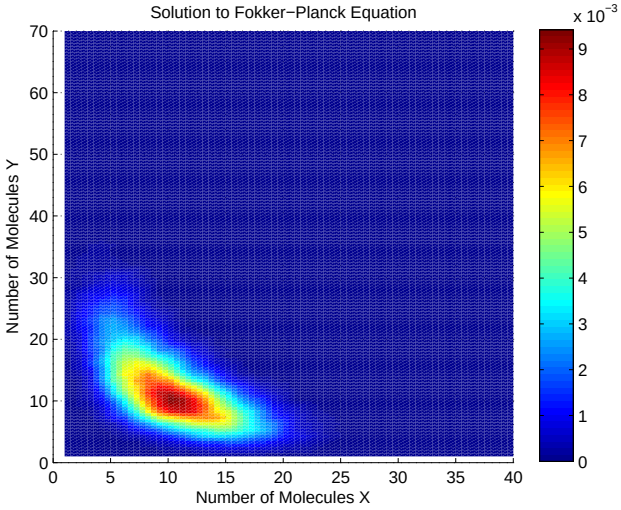

Figure 3.2: *The solution to the Fokker Planck equation (2.22) restricted to the subdomain* $(0, 40) \times (0, 70)$.

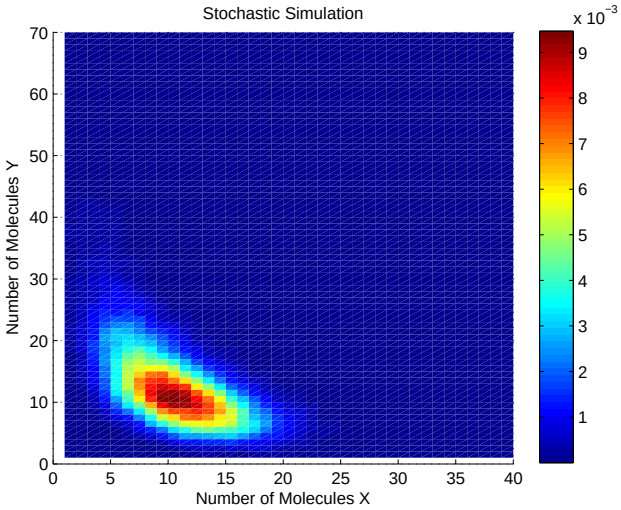

Figure 3.3: *Stationary distribution of (3.29) obtained by the Gillespie's simulation algorithm from Section 2.2.2*

Chapter 4

Modeling of the Influenza Reactions

In this chapter, we use our accumulated knowledge from modeling in cell biology from the second chapter. We study a chemical system represented by infected human cells with the influenza virus. Anthony (1998), Solomon (2001) and Erban et al. (2009) serve as the main references for our problem. After analyzing this problem, we define parametric equations for the main relations such as the associations between fever and the rate constant, the fever and the duration of fever and the rate constant and the duration of fever. Then we describe this problem using five chemical reactions where the previously mentioned parametrized relations are used. Due to the complexity of this problem, we need to take into account a new type of reaction constant which is also depending on time. Therefore, we modify our Monte Carlo simulation algorithm and we also reprogram and recompute the solution to the ordinary differential equations. We describe this problem by a system of ordinary differential equations (4.5), (4.6) and we compare the solution to this system with the stochastic simulation, see Figure 4.2. At the end of the chapter, we formulate this complex problem in terms of the stochastic differential equation with random coefficients. We also suggest two problems that arise from such a definition and that may be interesting for future research.

4.1 Description of the Problem

In order to keep reactions stable in cells, cells regulate the rate of reactions with enzymes, which are biological catalysts that increase the speed of chemical reactions without being consumed by the reactions. To keep the reaction-constant stable we need a constant temperature under which enzymes maintain their properties. Nevertheless, as the temperature increases, the rate of reactions can also increase, resulting in more molecular collisions. For the human body, which is the aim of our research, the rate of reactions increases with temperature in the following way: Higher temperatures lead to protein denaturization, wherein the activity of the enzyme becomes zero due to changes in the protein folding. Thus, in the case of human enzymes, we can see optimal activity at body temperature and no activity at very high temperatures. Suppose a case in which a human body is invaded by an influenza. This attack has a direct impact on enzymes (Solomon, 2001). One of the consequences of such an invasion of a human body by the influenza can be a temperature increase of the human body. Whether the temperature increases or not depends on the immunity system and the type of the virus. For Markovian time η, τ and ζ, we define stochastic intervals $[\eta, \tau[$,$[\tau, \zeta[$ in

the following manner

$$\begin{aligned}[\eta, \tau[&= \{(t, \omega) \in \mathbb{R}_+ \times \Omega; \eta(\omega) \leq t < \tau(\omega)\} \\ [\tau, \zeta[&= \{(t, \omega) \in \mathbb{R}_+ \times \Omega; \tau(\omega) \leq t < \zeta(\omega)\}.\end{aligned} \tag{4.1}$$

This stochastic interval can be interpreted in the following manner. The period that starts with the invasion of the human body by the influenza virus and ends with the defeat of the immunity system can be characterized by a stochastic interval $[\eta, \tau[$. This period is known, in medical terminology, as the incubation period. The duration of the influenza is not easily tractable so as a proxy, we use the duration of fever above 37°C, which is denoted as $[\tau, \zeta[$. The duration of these periods depend on the health of the human being. According to clinical study [Jefferson, et al. (2012)], we decide to approximate period $[\eta, \tau[$ with Weibull distribution with shape parameter $k = 3.1$ and scale parameter $\lambda = 0.1$ and period $[\tau, \zeta[$ with Weibull distribution with shape parameter $k = 4.15$ and scale parameter $\lambda = 0.005$.

Finally, the above mentioned problem can be characterized by simple chemical reactions given by:

$$\begin{gathered}\emptyset \xrightarrow{\lambda(t)} X + 2Y \qquad X + Y \xrightarrow{\mu} \emptyset \qquad 2X \xrightarrow{\theta_1} Y \\ 2Y \xrightarrow{\theta_2} 3X \qquad X \xrightarrow{\theta_3} Y\end{gathered} \tag{4.2}$$

Chemical reactions corresponding to the system (4.2) are listed in Table (4.1). As the tem-

Type	Reaction Rate	Chemical Reaction
Synthesis	$\lambda(t)$	$\emptyset \xrightarrow{\lambda(t)} X + 2Y$
Bimolecular reactions	μ	$X + Y \xrightarrow{\mu} \emptyset$
Degradation	θ_1	$2X \xrightarrow{\theta_1} Y$
	θ_2	$2Y \xrightarrow{\theta_2} 3X$
	θ_3	$X \xrightarrow{\theta_3} Y$

Table 4.1: Reactions of the chemical model (4.2).

perature rises, the enzymes activity increases until it reaches an optimal temperature. The enzymes activity abruptly falls after the optimal temperature is exceeded because the enzymes are protein denatureate. The optimal activity in a human body is about 38°C. There is no activity at very high temperatures. We approximately describe the effect of temperature on the enzymes activity call synthesis in the following manner

$$\lambda(z) = \begin{cases} a_0 & z \in [36, 37] \\ b_0 + b_1 z + b_2 z^2 + b_3 z^3 & z \in [37, 38] \\ c_0 + c_1 z + c_2 z^2 & z \in [38, 42.5] \end{cases}$$

We assume constant behavior for degradation rate μ and bimolecular reaction rates θ_1, θ_2 and θ_3.

There are several main phases of the evolution of fever during the infection of influenza in a human body [Anthony (1998)]. Surely, these phases are different for particular types of influenza. We categorized the main phases into two stages. We define the first stage as

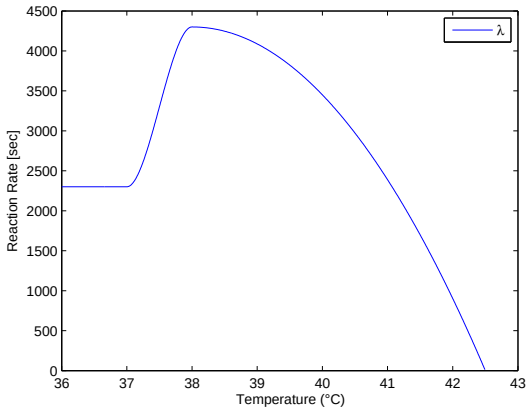

Figure 4.1: *The effect of temperature on enzymes activity is represented by rate-constants* $\lambda(t)$.

the period during which the temperature first reaches the optimal human body temperature during influenza, namely 38°C. The second stage is approximately the period during which the fever stabilizes under 38°C for the first time. Naturally, the fever considerably oscillates around its trend. In order to ameliorate our perception of the process, we simulate the duration of fever in MATLAB. We fitted the evolution of fever in a human body during influenza by a cubic spline

$$Y(t) = d_0 + d_1 t + d_2 t^2 + d_3 t^3. \tag{4.3}$$

The trajectory of the fever duration obtained by simulation is depicted in Figure 4.2. We fitted this trajectory using equation (4.3), see the red line in Figure 4.2. In the left panel of

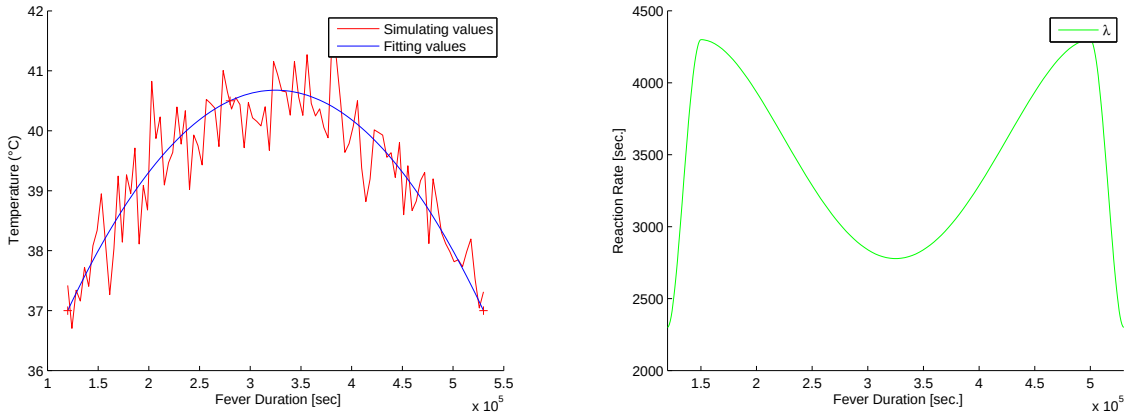

Figure 4.2: (Left) *The evolution of fever in a human body. (Red Line) shows the simulated values of fever. (Blue Line) shows its fitted value.* (Right) *In this picture we can see the enzyme activity during fever represented by rate-constant* $\lambda(t)$

Figure 4.2, we present the evolution of the rate-constant $\lambda(t)$ during fever, which we express by the following composite function

$$\lambda(z) \circ Y(t) = \lambda(Y(t)). \tag{4.4}$$

The evolution of the state represented by the number of molecules is described by $\mathbf{X} = [X, Y]$, where $X(t)$ is the number of molecules x of the chemical species and $Y(t)$ is the number of molecules y in the chemical system (4.2). Suppose that our chemical system contains enough molecules of x and y, then we can describe the time evolution of x and y by the ordinary differential equation model. The chemical system (4.2) can be described, up to the defeat of the immunity system i.e. at the interval $[\eta, \tau[$, in the following form

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - \mu xy - 2\theta_1 x^2 + 2\theta_2 y^2 \qquad \frac{\mathrm{d}y}{\mathrm{d}t} = \lambda - \mu xy + 2\theta_1 x^2 - 2\theta_2 y^2, \tag{4.5}$$

During the influenza, some chemical reactions can change their behavior [Jefferson, et al. (2012)]. For instance they can change the number of produced molecules. In order to reflect this property in chemical system (4.2), the chemical reaction θ_1 is replaced by the reaction θ_3. Therefore, the chemical system (4.2) is described at the interval $[\tau, \zeta[$, in the following manner

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda(t) - \mu xy - 2\theta_2 y^2 - \theta_3 x \qquad \frac{\mathrm{d}y}{\mathrm{d}t} = \lambda(t) - \mu xy - 2\theta_2 X_2^2 + \theta_3 x, \tag{4.6}$$

The rate constants were chosen as follows:

$$\lambda_1 = 2300, \quad \mu = 3.5, \quad \theta_1 = 0.25, \quad \theta_2 = 1.4, \quad \theta_3 = 0.52. \tag{4.7}$$

4.2 Numerical Solution of the Evolution of the Influenza

Let us consider two chemical species X and Y which are in a reactor of volume V and which are subjected to a set of five chemical reactions (4.2). Let $X(t)$ and $Y(t)$ be the number of molecules of the chemical species X and Y, respectively. The concentration of X (resp., Y) will be denoted by $x = \frac{X}{V}$ (resp., $y = \frac{Y}{V}$). In order to be able to describe the time evolution of x and y by the ordinary differential equations (4.5) and (4.6), we need to have enough molecules of X and Y in the system and they ought to be well-mixed. Then the stochastic model of the chemical system (4.2) can be obtained using the Gillespie's stochastic algorithm. Again, we scale the rate constants with the appropriate power of the volume V as it seen below:

$$\lambda = \lambda_1(t)V, \qquad \lambda_2 = \frac{\mu}{V}, \qquad \theta_1 = \frac{\theta_1}{V^2}, \qquad \theta_2 = \frac{\theta_2}{V} \qquad \theta_3 = \frac{\theta_3}{V}. \tag{4.8}$$

Then the propensity function of the particular reactions are given as the product of the scaled rate constant and numbers of available reactant molecules, namely,

$$\begin{aligned} \alpha_1(x, y) =& \lambda(t), \qquad \alpha_2(x, y) = \mu xy, \qquad \alpha_3(x, y) = \theta_1 x(x-1), \\ & \alpha_4(x, y) = \theta_2 y(y-1), \qquad \alpha(x, y) = \theta_3 x. \end{aligned} \tag{4.9}$$

Using equations of ordinary differential systems (4.5), (4.5) and the Gillespie's algorithm from Section 2.2.2, we can simulate the stochastic trajectories of (4.2). To solve this influenza problem, we first simulate trajectories by Gillespie's algorithm described in Section 2.2.2 of chemical system (4.2) with reactions λ, μ, θ_1 and θ_2 during the incubation period $[\eta, \tau[$. We choose the length of this period to be 2 days which is the mean duration of this period according to reference [Anthony (1998)]. From the deterministic point of view, we solve this system (4.5) of ordinary differential equations with the initial condition $[X, Y] = [0, 0]$. We use these parameter values (4.7) for coefficients λ, μ, θ_1 and θ_2.

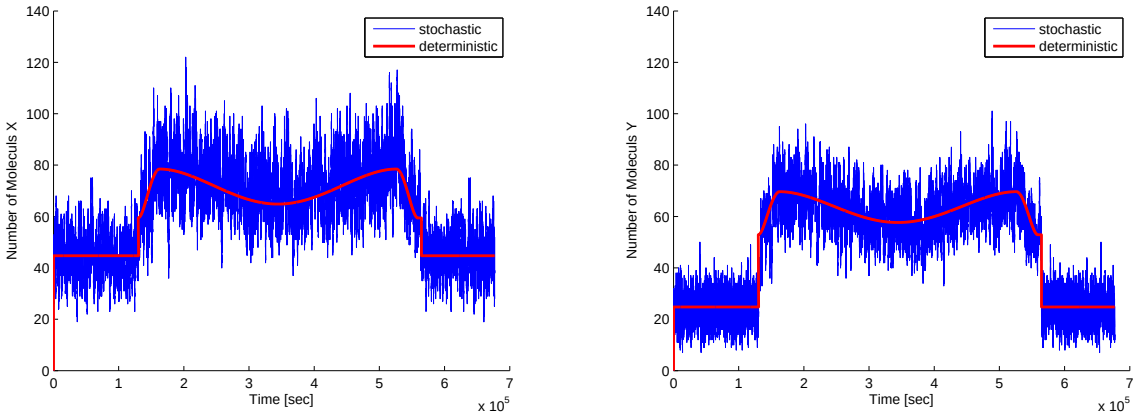

Figure 4.3: *One realization of Stochastic simulation algorithm for the system of chemical reactions (4.2) (blue line) and the solution of the deterministic ODE (4.5) and (4.6) (red line). (Left) The number of molecules of X as a function of time over the whole duration of influenza (9 days) i.e from time to invasion to human body up to defeat of the immunity system. Third part of scale is reverse defeated influenza by immunity system. (Right) Time evolution of molecules Y during the whole period of the influenza virus.*

Second, we simulate by modified Gillespie's algorithm chemical system (4.2) with chemical reactions λ_t, μ, θ_1 and θ_3. The length of the simulation period was chosen as a mean length of the influenza duration which is six and half days [Jefferson, et al. (2012)]. We choose initial conditions $[X, Y] = [43, 27]$ due to keeping continuous trajectories. Again, from deterministic point of view, we solved system (4.6) of ordinary differential equations. We use parameter values (4.7) for coefficients μ,θ_1, θ_3 and for coefficient $\lambda(t)$ we use parametric equation (4.4). In Figure , we compare the time evolution of X and Y given by the stochastic Gillespie's algorithm with deterministic differential equations (4.5) and (4.6). We can see after 1.2×10^5 seconds rapid growth of molecules X and Y. This growth is caused by defeating immunity system. After 4.3×10^5 seconds, on the contrary, immunity system defeats the influenza virus. Consequently, the number of molecules rapidly decreases to a stable state. According to the assumptions, the number of molecules X and Y reach its peak shortly after defeating immunity system and also at the of the duration of influenza. This corresponds with optimal temperature for fighting with the influenza virus [Jefferson, et al. (2012)].

4.3 Langevin Equation with Random Coefficients for Chemical System (4.2)

In this section, we formulate the Langevin equation which describes the chemical system of the infected cell by influenza (4.2). This formulation should serve as a motivation for future research.

Let $W(\cdot)$ be a one-dimensional Brownian motion. Suppose that $(\Omega, \mathcal{F}, (\mathcal{F}_t), \mathrm{P})$ is a stochastic basis with filtration which satisfies conditions from Chapter 3. Assume $T > 0$ is given, and $b : \Omega \times [0, T] \times \mathbb{R}^2 \to \mathbb{R}^2$ and $\sigma : \Omega \times [0, T] \times \mathbb{R}^2 \to \mathbb{R}^{2\times 1}$ are given measurable functions for which the following properties hold:

I $\exists K\ \forall\omega \in \Omega\ \forall t \in [0,T]\ \forall x,y \in \mathbb{R}^2$

$$\|b(t,x) - b(t,y)\| \vee \|\sigma(t,x) - \sigma(t,y)\| \leq K(\omega)\,\|x-y\|\,. \tag{4.10}$$

where $K(\omega)$ is random variable.

II For all $\omega \in \Omega$ the mapping $x \mapsto \sigma(\omega, x)$ is of class C_b^2 i.e., it has bounded and continuous derivatives of first and second order.

Let τ and ζ are Markov times. We define the following sets: $A = \{[x,y] \in \mathbb{R}^2; x \geq 0, y \geq 0\}$ and $S = \{[x,y] \in \mathbb{R}^2\} \backslash A$. Consider the following stochastic differential equation of chemical system (4.2):

$$X(t) = X_0 + \int_0^t \underline{(}s, X(s))\mathrm{d}s + \int_0^t \sqrt{2\sigma(s, X(s))}\mathrm{d}W \tag{4.11}$$

where the drift and diffusion coefficients are

$$b_x(t,x,y) = \begin{cases} \lambda - \mu xy - 2\theta_1 x(x-1) + 2\theta_2 y(y-1) & t_0 \leq t < \tau \\ \lambda(t) - \mu xy + 2\theta_2 y(y-1) - \theta_3 x & \tau \leq t < \zeta \end{cases}$$

$$b_y(t,x,y) = \begin{cases} \lambda - \mu xy + 2\theta_1 x(x-1) - 2\theta_2 y(y-1) & t_0 \leq t < \tau \\ \lambda(t) - \mu xy + 2\theta_2 y(y-1) + \theta_3 x & \tau < t \leq \zeta \end{cases}$$

$$\sigma_x(t,x,y) = \begin{cases} \sqrt{\lambda - \mu xy + 2\theta_1 x(x-1) + 2\theta_2 y(y-1)} & t_0 \leq t < \tau, \quad [x,y] \in A \\ \sqrt{\lambda(t) - \mu xy + 2\theta_2 y(y-1) + \theta_3 x} & \tau < t \leq \zeta, \quad [x,y] \in A \\ \sqrt{\lambda} & t_0 \leq t \leq \zeta, \quad [x,y] \in S \end{cases}$$

$$\sigma_y(t,x,y) = \begin{cases} \sqrt{\lambda + \mu xy + 2\theta_1 x(x-1) + 2\theta_2 y(y-1)} & t_0 \leq t < \tau, \quad [x,y] \in A \\ \sqrt{\lambda(t) + \mu xy + 2\theta_2 X_2(y-1) + \theta_3 x} & \tau < t \leq \zeta, \quad [x,y] \in A \\ \sqrt{\lambda} & t_0 \leq t \leq \zeta, \quad [x,y] \in S \end{cases}$$

We assume that the existence of the solution to equation (4.11) should be ensured by the following theorem:

Theorem 4.3.1 (Existence of the Solution)**.** Let $b : \Omega \times [0,T] \times \mathbb{R}^2 \to \mathbb{R}^2$ and $\sigma : \Omega \times [0,T] \times \mathbb{R}^2 \to \mathbb{R}^{2\times n}$ be measurable functions satisfy hypotheses (I) and (II). Then there exists a solution X to equation (4.11).

Proof. See [Kohatsu-Higa (1997)]. □

We consider the solution to the equation (4.11) to be a 2-dimensional continuous process X such that $\sigma(s, X(s))$ is Stratonovich-integrable with respect to W see [Kohatsu-Higa (1997)]. We believe that the equation (4.11) could be expressed as the Fokker-Planck equation with random variables. Nevertheless, we would need a much more advanced theory for such a problem. Hence, we propose the derivation of the Fokker-Planck equation from the equation (4.11) and its numerical computation for further research.

Conclusion

We presented the key methods used for modeling the number of molecules in cell biology with focus on the computation of the transition probability function and the density of the invariant measure. The key methods that describe the time evolution of the number of molecules in a cell were given in Chapter 2. They include the system of the ordinary differential equation, the master equation, the Langevin equation, the Fokker-Planck equation and the Monte Carlo simulation represented by Gillespie's simulation algorithm. We formulated two types of chemical system for which we were able to apply the mentioned methods. The first chemical system was a one-dimensional chemical switch and the second was the synthesis between two molecules. Then we compared the numerical solutions to the system of the ordinary differential equations with the results from the Monte Carlo simulation and with the solution to the Fokker-Planck equation in the dynamic case. The figures suggests that the results coincide since the Monte Carlo simulations oscillate around the solution to the ordinary differential equations. Moreover, the oscillation of the Monte Carlo simulations corresponds to the dynamic evolution of the transition probability function.
Furthermore, we showed, based on the theories presented in Chapter 3, that the numerical computations of the transition probability functions for both chemical systems in Chapter 2 were correct. In order to reach this conclusion, we needed to formulate and verify the necessary and sufficient conditions for the existence of the solution which is a Markov process with transition probability function. Since one of the main aims in cell biology is also to solve for the density of the invariant measure, the theory of the invariant measure was introduced in Chapter 3. After the verification of the existence of the density, we numerically computed this density as the solution to the Fokker-Planck equation in a stationary case. When we compared these solutions with results from the Monte Carlo simulations, we found that they are almost identical.
In the last chapter, we defined our own problem describing the infection of a human cell by an influenza. In comparison to a common chemical system which has a constant reaction rate, our problem is more complex because the reaction rate is dependent on time. In addition the reactions in this chemical system change at a random time. We simplified this problem by assuming that the time is deterministic. We obtained the results using Monte Carlo simulation for this simplified problem. Our results show that the number of molecules in the system is the highest when the temperature attains 38°C. This is in fact consistent with numerous medical studies that are concerned with the behavior of enzymes in the human body during the influenza infection. At the end of this chapter, we formulated this complex problem in terms of the stochastic differential equation with random coefficients. We also suggested two problems that arise from such a definition and that may be interesting for future research.
The literature that we drew most inspiration from for Chapter 2 was: [Kampen (1992)], [Hoffman (2001)], [Hoffman (2001)] and [Sjöoberg, et al. (2009)]. For Chapter 3, [Khasminskii

(2011)], [Strook (2005)], [Soize (1994)] and [Seidler (2011)] served as the main reference. In the last chapter, we obtained the most important inspiration for the formulation of our own problem from [Anthony (1998)], [Solomon (2001)], [Jefferson, et al. (2012)] and [Erban et al. (2009)].

Notation

$(\Omega, \mathcal{F}, (\mathcal{F}_t), \mathrm{P})$	the filtered probability space
$\mathbb{R}^m$	m-dimensional Euclidean space
$\mathbb{R}^+$	the non-negative real numbers
$\mathbb{R}^{m\times n}$	the $n \times m$ matrices
C^2	the class of functions twice continuously differentiable
$\mathcal{F}_t$	σ-algebra generated by $\{W_s; s \leq t\}$
$s \wedge t$	the maximum of s and t
U_R	$= \{x : \lvert x\rvert < R\}$, the ball
$\mathcal{B}$	σ-algebra of Borel sets in Euclidean space
$\mathbb{1}_A(\cdot)$	indicator function of the set A

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